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European Journal of Pharmaceutics and Biopharmaceutics 70 (2008) 226–233
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Specific interactions between diphenhydramine and α-helical poly(glutamic acid) – A new ion-pairing complex for taste masking and pH-controlled diphenhydramine release

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Received 28 January 2008; accepted in revised form 7 April 2008
Available online 14 April 2008

Abstract

Formation of drug/excipient complex through ionic interactions has proven to be very effective for both controlled release and taste masking. Unfortunately, the ionic interactions between drugs and small molecule excipients are usually weak, and the stability of the formed complexes can be greatly influenced by solution ionic strength. In this study, we explored to formulate diphenhydramine (DPH), a very bitter tasting drug, using small molecular weight and carboxyl group containing polymers. Studies showed that DPH interacted with α-helical poly(glutamic acid) specifically to produce DPH/poly(glutamic acid) complexes, mostly spherical in shape with a diameter of around 1.0 μm. Other drugs with similar chemical structures as DPH, such as phenylephrine and pseudoephedrine, could not form complexes with poly(glutamic acid) or other polymers under the same conditions. Although DPH in DPH/poly(glutamic acid) complexes existed amorphously, it showed increased stability.*In vitro* studies using electronic tongue demonstrated that poly(glutamic acid) might be as effective as sucralose for DPH bitter taste blocking. In addition, DPH/poly(glutamic acid) complexes were not stable in neutral or weak acidic (pH > 5) environments and dissolved rapidly and completely. Therefore, DPH/poly(glutamic acid) complex may serve as a new formulation for taste masking and controlled DPH release in gastrointestinal tract. This is the first report that small molecule drugs can interact with peptides of specific secondary structures to form stable complexes. In addition to greatly expanded ion-pairing excipient pool, application of peptides in drug formulation may also solve the selectivity and stability problems faced by current small molecule excipients.

Keywords: Peptide; Formulation; Nanoparticles; Controlled release; pH-sensitivity; Taste masking

1. Introduction

Ion-pairing is a process that involves stoichiometric replacement of polar counter-ions (i.e., chloride, acetate, nitrate, etc.) in the drug with an ionic excipient of similar charge. Through ion-pairing complexation, the activity, solubility, cell permeability, and stability of drugs can be manipulated by using excipients with different chemical and physical properties [1–4]. Ion-pairing has been used in the pharmaceutical industry, mainly as an additional drug-delivery method, and has proven to be a very effective mean for controlled drug release and taste masking [5–8]. Unfortunately, since only small molecule excipients have been used in ion-pairing complexation, the interactions between drugs and excipients are weak, and the stability of formed complexes can be greatly influenced by solution ionic strength [7]. In a recent study, the ion-pairing ability of a carboxyl groups containing polyelectrolyte (carbomer) was tested [2]. A basic (positively charged) drug, procaine,

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doi:10.1016/j.ejpb.2008.04.004

was dispersed in the carbomer solution to form procaine-carbomer ion pair complexes. Because of blocked hydroxyl ion (OH^-) access to procaine in the formed ion pairing complexes, the stability of procaine in procaine-carbomer complexes was increased 4–6 times compared to free procaine in the reference solutions. Since extremely high molecular weight carbomer (3000 kDa) was used, carbomer in the solution existed as hydrogels. Therefore, the role of carbomer in that study is more like an ion-exchange resin [9,10].

Carboxyl groups containing compounds have been widely used in drug formulation [8]. The advantage of carboxyl groups can be attributed to their ability to form strong ionic interactions with drugs of interest because they are excellent hydrogen bond donors and have accepting sites. In this study, we explored the possibility of using small molecular weight ($M_w = 1.0$–40 kDa) and carboxyl groups containing polymers to form stable ion-pairing complexes with basic (positively charged) drugs. We found that poly(glutamic acid) in α-helical conformation interacted with diphenhydramine (DPH, a very bitter drug) specifically to form stable ion-pairing complexes. Under the acidic conditions, these DPH/poly(glutamic acid) complexes could further self-assemble into aggregates of spherical shapes. The pH-controlled DPH/poly(glutamic acid) complex dissolution and the potential applications of DPH/poly(glutamic acid) complexes in taste masking and controlled DPH release were also tested *in vitro*.

2. Materials and methods

2.1. Materials

Diphenhydramine HCl, Phenylephrine HCl, and Pseudoephedrine HCl were supplied by Kongo (Toyama, Japan), Boehringer Ingelheim (Ingelheim, Germany), and BASF (Minden, German), respectively. Poly(aspartic acid), poly(glutamic acid), and poly(maleic acid) of various molecular weights were purchased from Sigma–Aldrich (St. Louis, Missouri).

2.2. Preparation of drug/polymer complexes

Drugs were dissolved in 40 ml of 0.2 M sodium phosphate buffer (NaPB, pH 3.0) solution of various concentrations. Polymer stock solutions in the same NaPB were added into the drug solutions to form drug/polymer mixtures. These drug/polymer mixtures were incubated at 4 or 25 °C for up to 48 h. Interactions between drug and polymers were studied using UV spectrophotometry (μQUANT, Bio-Tek Instruments, Winooski, Vermont) by comparing the spectra changes of drugs in the range of 260–270 nm. Formation of drug/polymer complexes was estimated by monitoring solution absorbance (turbidity) changes at 500 nm. Drug/polymer complexes were collected by centrifugation (11,000 rpm for 15 min). The free drug in the supernatant was estimated by spectrophotometric analysis using the standard curves prepared from pure drugs. Collected drug/polymer complexes were washed with the same NaPB (0.2 M, pH 3.0) and then dried on a vacuum centrifuge (Vacufuge, Eppendorf, Westbury, New York).

2.3. Physical characterization

2.3.1. SEM

The morphology of DPH/poly(glutamic acid) complexes was examined using a scanning electron microscope (SEM) (LEO Electron Microsopy, Thornwood, New York). A current of 2394 mA, voltage of 1.00 kV and a working distance of 5.0 mm were applied. The particular SEM utilized a field emission gun (FEG) as the electron source. Consecutive magnifications (200×, 1000×, 3000×, 10,000×, and 30,000×) were used to view the morphology of formed DPH/poly(glutamic acid) complexes.

2.3.2. DSC/TGA

The differential scanning calorimetry (DSC) thermogram of DPH/poly(glutamic acid) complexes was recorded on DSC Q100 (TA Instruments Inc., New Castle, Delaware) and compared with DSC thermograms of the pure drugs, peptides, and drug/peptide complexes. The scanning rate was controlled at 10 °C/min with the starting and ending temperature at 35 and 300 °C, respectively. The heat capacity was calculated by using sapphire as the reference. Thermogravimetric analysis (TGA) were also performed on TGA Q50 (TA Instruments Inc., New Castle, Delaware) with a starting and ending temperatures of 25 and 400 °C, respectively.

2.3.3. X-ray diffraction crystallography

The X-ray crystallographic patterns of DPH, poly(glutamic acid), and DPH/poly(glutamic acid) complexes were studied using an X-ray Diffractometer (Rigaku, Tokyo, Japan). Samples were pressed into circular form on a quartz sample holder, and scanned from 0 to 60°. A Bragg angle of 2θ was recorded at a scan rate of 1.0°/min.

2.3.4. Circular dichroism

The CD spectra of poly(glutamic acid) in the presence and absence of DPH at different pHs were recorded on a JASCO 710 spectropolarimeter (Tokyo, Japan). Samples were dissolved in 20 mM sodium acetate [11]. The scanning wavelength ranged from 190 to 250 nm at the interval of 1.0 nm.

2.4. The pH-controlled DPH/poly(glutamic acid) complex dissolution

Prepared DPH/poly(glutamic acid) complexes were re-suspended in 0.2 M NaPB solutions of various pHs (pH 3, 5.5, 7.0) and incubated at room temperature. Solution samples were collected at different time intervals and then centrifuged at 11,000 rpm for 2.0 min to remove

un-dissolved DPH/poly(glutamic acid) complexes. The free DPH released into the supernatants was estimated using the spectrophotometric analysis and was plotted as a function of time to determine the dissolution kinetics.

2.5. Taste masking tests

The taste masking efficiency of DPH/poly(glutamic acid) complexes was tested *in vitro* using Electronic tongue (E-tongue). The electronic tongue is an instrument that measures and compares tastes of solutions [12,13]. The Electronic Tongue mirrors the three levels of biological taste recognition: the receptor level (probe membranes in the E-tongue mimics the taste buds in humans); the circuit level (transducer mimics the neural transmission in humans); and the perceptual level (computer and statistical analysis mimics the cognition in the human thalamus). This technique compresses timelines and lets researchers gather taste and dissolution data simultaneously [12,13]. The Electronic Tongue system (Alpha M.O.S., France) used in this study consists of an array of seven sensors and a 16-position autosampler. All sample solutions were prepared and analyzed immediately the day after sample preparation. In the same testing run, sucralose solution (0.5 mg/ml) and sucralose solution (0.5 mg/ml) with 1.0 mg/ml DPH were also tested for comparison. The sensors were calibrated with 0.01 M HCl prior to measurement and the diagnostic test conducted prior to sample measurement with 0.01 M HCl, sodium glutamate, and NaCl solutions. A measurement of the electrical potential difference between each sensor and the reference electrode at room temperature was conducted. Each sample was measured by the sensors for 2 min, and a 30 s rinse in water was used to separate the different sample measurements. The series of sample measurements was repeated four times to get an average reading. The result was analyzed by the Alpha M.O.S. Astree II software. Measured potential results were treated by multivariate statistical methods, and the data was plotted on a principal component analysis (PCA) map. The distance between a pair of data cluster was then determined to assess the similarity in taste profile between the pair of samples.

3. Results and discussion

3.1. Specific interaction between DPH and α-helical poly(glutamic acid)

Three carboxyl group containing polymers (Fig. 1), including poly (aspartic acid), poly (glutamic acid), and poly (maleic acid) of various molecular weights (1000–40,000 Da), were tested for their complexation abilities with DPH at different pHs (Table 1). Among these three polymers, only poly(glutamic acid) can interact with DPH to form DPH/polymer complexes under a very acidic condition (pH 3.0). Formed DPH/poly(glutamic acid) complexes are mostly spherical in shape with a diameter of about 1–2 μm as observed under scanning electron microscopy (SEM) (Fig. 2). The complexation of DPH and poly(glutamic acid) was associated with solution turbidity and thus could be monitored by measuring the solution absorbance changes at 500 nm.

The complexation abilities of poly(glutamic acid) with other two drugs, phenylephrine and pseudoephedrine, were also tested. Despite their similar chemical structures to DPH (Fig. 1), neither phenylephrine nor pseudoephedrine form the same complexes with poly(glutamic acid) in a wide pH range, from pH 3.0 to 7.2 (Table 1), implying that the interaction between DPH and poly(glutamic acid) is specific. Results from CD studies showed that poly(glutamic acid) experienced a conformation transition, from random coil to α-helix (Fig. 3a), as the solution pHs were changed from pH 7.2 to 3.0. This conformation transition of poly(glutamic acid) happens in a narrow pH range (pH 3.5–4.5) which match the pK_a value of the side chain carboxyl group (p$K_a = 4.1$) of glutamic acid. Therefore, carboxyl group protonization reduced side chain repulsions should be the driving force for α-helical poly(glutamic acid) formation at acidic pHs. It is interesting to note that there is a very close correlation between the α-helical contents of poly(glutamic acid) and DPH/poly(glutamic acid) complex formation (Fig. 3b). Therefore, adapting α-helical structure seems to be an essential step for poly(glutamic acid) to interact with DPH to form DPH/poly(glutamic acid) complexes specifically.

To further study the interaction between DPH and α-helical poly(glutamic acid), DPH and poly(glutamic acid) was mixed in two different ways: (a) pre-mixing DPH and poly(glutamic acid) at pH 7.2 and then adjusting solution to pH 3.0; (b) adding DPH dropwise into pH 3.0 poly(glutamic acid) solution. Uniform DPH/poly(glutamic acid) complexes were obtained in both cases (data not shown). Addition of DPH into pH 3.0 poly(glutamic acid) solution only caused slight CD spectrum shift but could not disrupt the α-helical structures of poly(glutamic acid) (Fig. 4). This result confirms that DPH/poly(glutamic acid) complexation is from the direct interaction between DPH and α-helical poly(glutamic acid).

Poly(glutamic acid) molecular weight and poly(glutamic acid): DPH ratios affected.

DPH/poly(glutamic acid) complexation was also studied. The molecular weight of poly(glutamic acid) affects both the kinetics and the equilibrium of DPH–poly(glutamic acid) complexation. At a fixed poly(glutamic acid): DPH ratio of 4% (w/w), the 13 kDa poly(glutamic acid) shows the best DPH complexation efficiency, followed by poly(glutamic acid) with molecular weight of 1.5 kDa. Poly(glutamic acid) with a molecular weight of 44 kDa only shows an initial rapid formation phase without the slow complex growth phase. In addition, poly(glutamic acid): DPH ratio also affects DPH/poly(glutamic acid) complex formation (Fig. 5B). Increased poly(glutamic acid): DPH ratio is associated with improved complexation kinetics and efficiency. However, there is an optimal

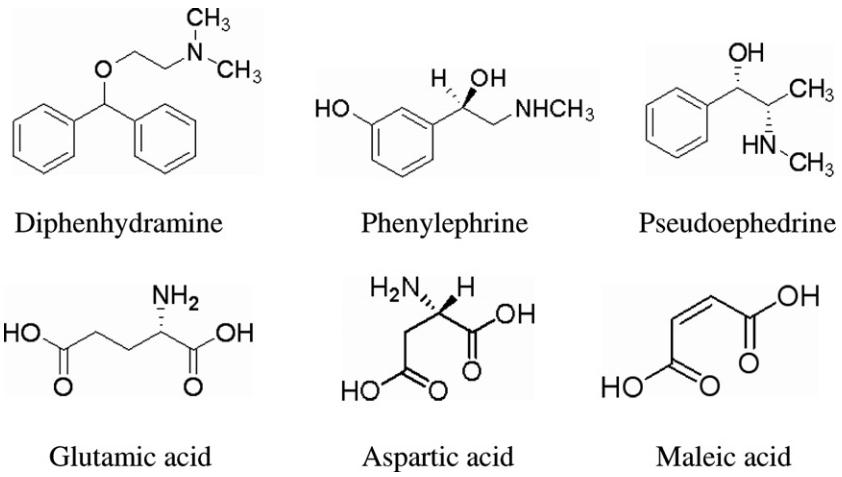

Fig. 1. Structures of drugs and carboxyl group containing monomers.

Table 1
Complexation of polymers with drugs at different pHs

	Poly-aspartic acid	Poly-glutamic acid	Poly-maleic acid
Diphenhydramine			
pH 3.0	–	Yes	–
pH 5.0	–	–	–
pH 7.2	–	–	–
Phenylephrine			
pH 3.0	–	–	–
pH 5.0	–	–	–
pH 7.2	–	–	–
Pseudoephedrine			
pH 3.0	–	–	–
pH 5.0	–	–	–
pH 7.2	–	–	–

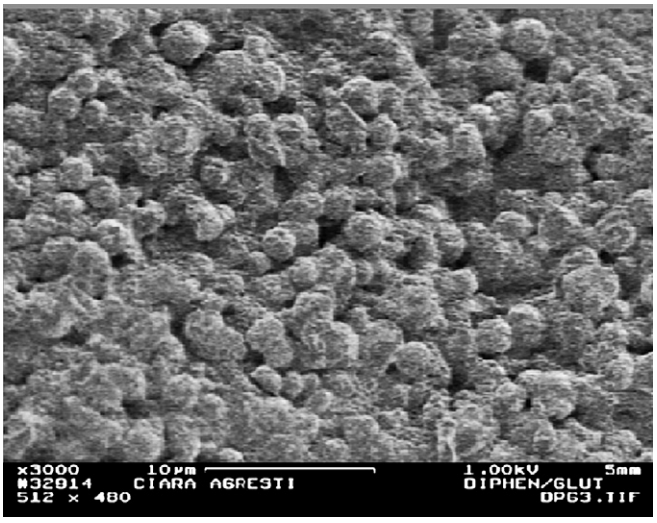

Fig. 2. SEM images of DPH/poly(glutamic acid) complexes at 3000× magnification.

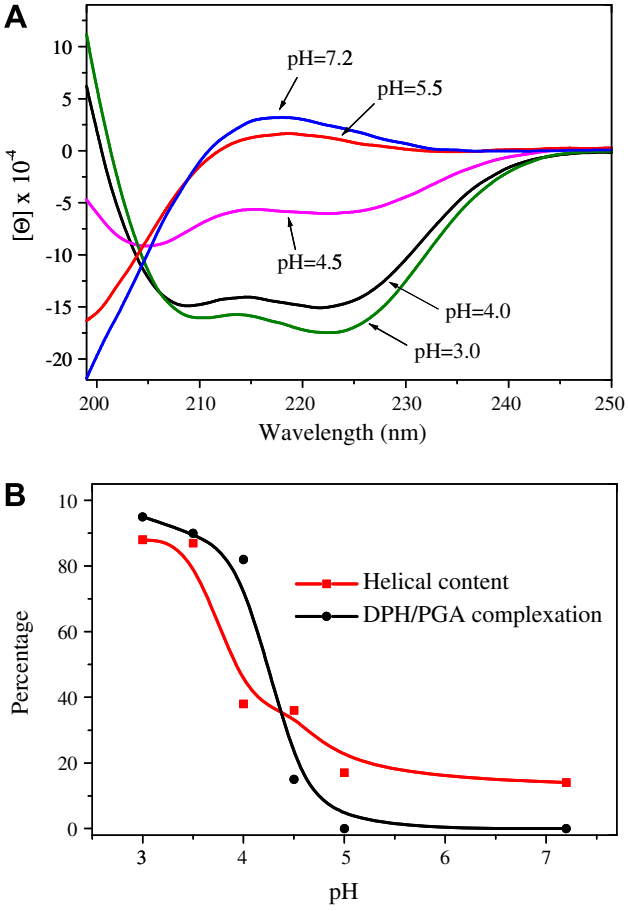

Fig. 3. (A) CD spectra of poly(glutamic acid) in 20 mM NaAc solutions at various pHs. (B) pH affected DPH/poly(glutamic acid) complexation (increased solution turbidity) and α-helical content changes in poly(glutamic acid).

poly(glutamic acid): DPH ratio (4–6% w/w) for DPH/poly(glutamic acid) complex formation.

DPH/poly(glutamic acid) complex formation is a biphasic process, an initial rapid formation phase right after poly(glutamic acid) is added, followed by a slow growth phase (Fig. 5a and b). It took 30 h for DPH and poly(glutamic acid) to accommodate each other to form the stable complexes in the solution (Fig. 5a and b). Therefore, it seems that in addition to the more specific interactions (slow phase), electrostatic interaction (rapid phase)

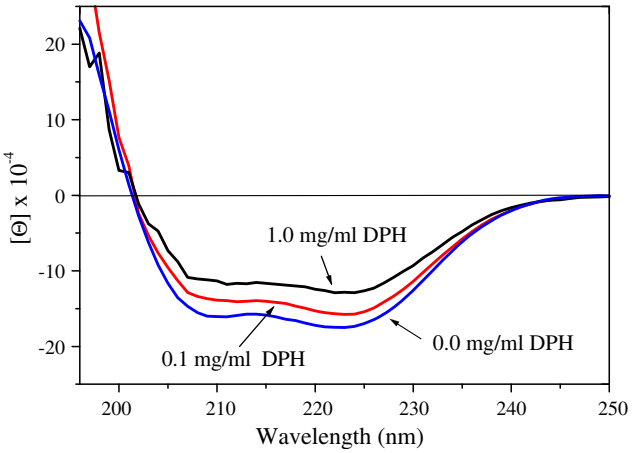

Fig. 4. Effects of DPH concentration (0–1.0 mg/ml) on the CD spectra of poly(glutamic acid) at pH 3.0.

between DPH and α-helical poly(glutamic acid) may also exist even though the electrostatic interaction should not be the predominant force between DPH and poly(glutamic acid) at acidic pHs. In the range of pH 3–7.2, the amine group in DPH will be protonated and exists in the form of NH_3^+. This NH_3^+ group can interact with the negatively charged domains (such as small amounts of un-protonated carboxyl groups) in poly(glutamic acid) and thus contribute to the electrostatic interaction between DPH and poly(glutamic acid).

As we know, the time for the coalescence of two particles is proportional to the fourth power of the radius and to the diffusion coefficient. Therefore, as primary complex particles grow, the particle mobility and excess surface free energy decrease, leading to a decrease of particle coalescence. As a result, DPH/poly(glutamic acid) complexes mainly grew via aggregation and the structure of the resulting micron sized particles is denoted as nano-structured as seen in Fig. 5d. The texture of these DPH/poly(glutamic acid) particles is granular, alluding to an agglomeration composed of nanosized particles (~100 nm). A correlation between increased DPH/poly(glutamic acid) complex sizes and the incubation time (Fig. 5c) supports our conclusion.

3.2. Characterization of DPH/poly(glutamic acid) complexes

Differential scanning calorimetry (DSC) was used to study the thermal properties of formed DPH/poly(glutamic

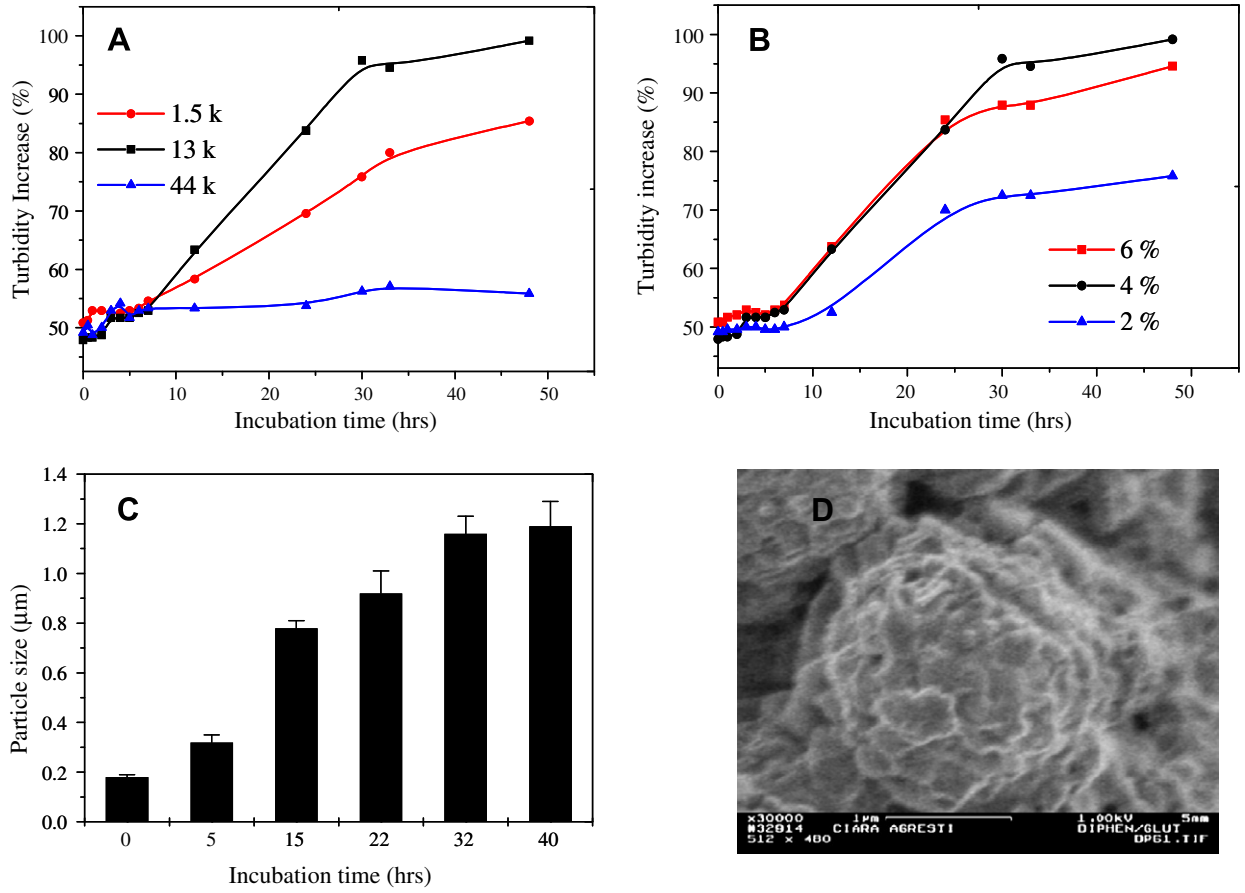

Fig. 5. (A) Poly(glutamic acid) molecular weights affected DPH/poly(glutamic acid) complexation. Poly(glutamic acid):DPH ratio = 4%; (B) Poly(glutamic acid):DPH ratios affected DPH/poly(glutamic acid) complexation. Poly(glutamic acid) molecular weight = 13 kDa; (C) Incubation associated particle size changes of DPH/poly(glutamic acid) complexes; (D) SEM images of DPH/poly(glutamic acid) complexes at 30,000× magnification.

acid) complexes. The obtained DSC diagrams from pure DPH, poly(glutamic acid), and DPH/poly(glutamic acid) complexes were simultaneously plotted for comparison. As shown in Fig. 6a, poly(glutamic acid) does not have any phase transition in the tested temperature range from 45 to 300 °C, while the pure DPH has an endothermic peak at 171 °C and an exothermic peak at 232 °C. According to literatures, the heat influx and efflux peaks of pure DPH correspond to the melting and decomposition points of DPH, respectively. In contrast, DPH/poly(glutamic acid) complexes show an endothermic peak at 238 °C and an exothermic peak at 245 °C, confirming that DPH interacts with poly(glutamic acid) specifically to form stable complexes.

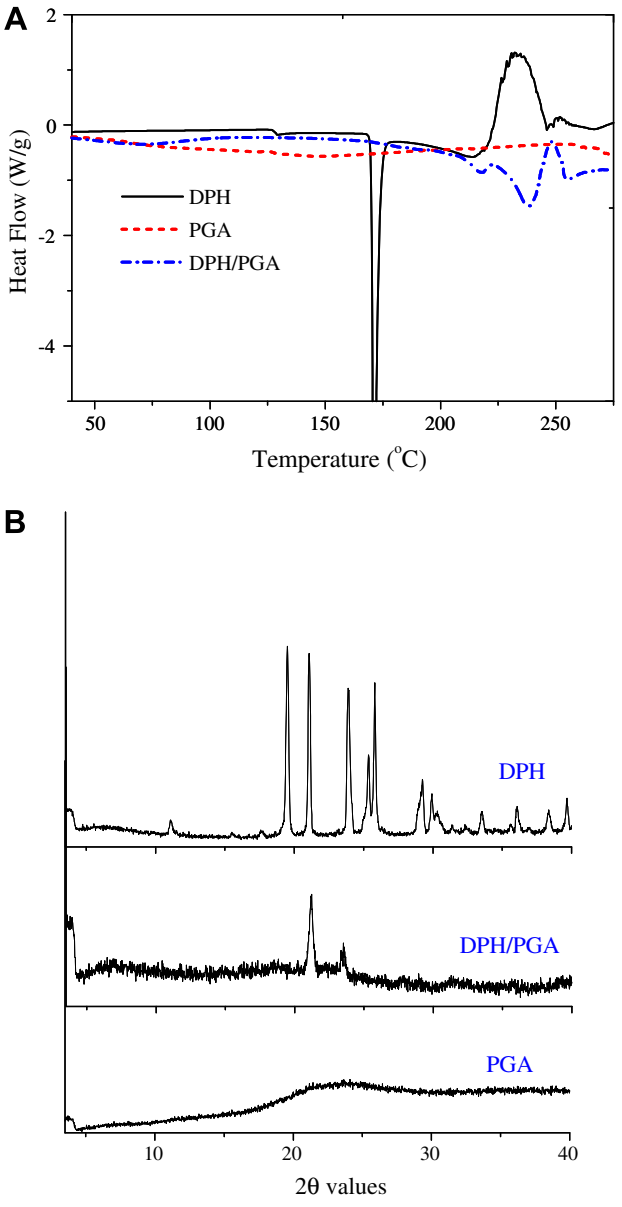

Fig. 6. The DSC (A) and wide angle X-ray diffraction (WAXS) patterns (B) of DPH, poly(glutamic acid), and DPH/ poly(glutamic acid) complexes.

In fact, carboxyl groups containing compounds have been widely used in crystal engineering processes [8]. The advantage of carboxyl groups can be attributed to their ability to form strong ionic interactions with drugs of interest because they are excellent hydrogen bond donors and have accepting sites. To further elucidate the interaction between DPH and poly(glutamic acid), the crystal characteristics of the DPH/poly(glutamic acid) complexes were examined using X-ray diffraction. Unlike pure DPH, the DPH/poly(glutamic acid) complexes display typical amorphous patterns (Fig. 6b). Therefore, the heat influx peak of DPH/poly(glutamic acid) complexes at ~238 °C may result from DPH/poly(glutamic acid) complex dissociation. The exothermic DSC peak of DPH/poly(glutamic acid) complex at 245 °C may be from the decomposition of free DPH which are just released from DPH/poly(glutamic acid) complex dissociation at 238 °C. Followed thermogravimetric analysis (TGA) results support this conclusion. Pure DPH completely decomposes when the temperature reaches 250 °C (Fig. 7). On the contrary, DPH in DPH/poly(glutamic acid) complexes is stable. About 50% of DPH/poly(glutamic acid) complexes are remained even when the samples are heated to 400 °C. The smooth TGA curve of DPH/poly(glutamic acid) reflects the heterogeneous nature of the interaction between DPH and poly(glutamic acid). In fact, in addition to the possible electrostatic interactions between the amino group of DPH and the carboxyl groups in poly(glutamic acid), the two phenyl groups of DPH should also participate in DPH/poly(glutamic acid) complexation by interacting with the hydrophobic domains on poly(glutamic acid) backbone, especially when poly(glutamic acid) forms α-helix.

3.3. The pH-controlled DPH release from DPH/poly(glutamic acid) complexes

As demonstrated above, DPH/poly(glutamic acid) complexation is a result of the direct interaction between DPH and α-helical poly(glutamic acid) (Figs. 3 and 4). Since

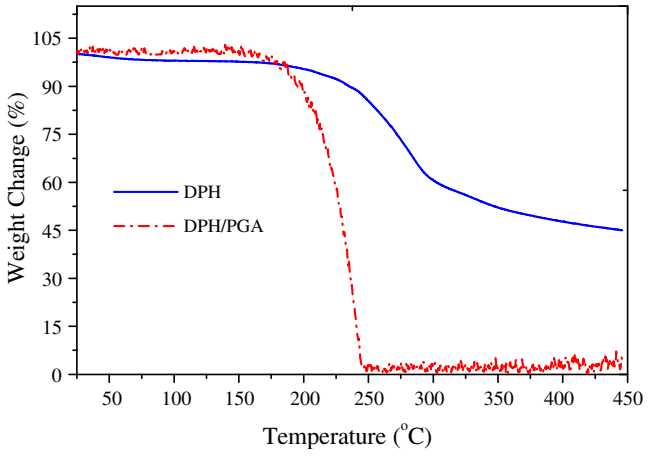

Fig. 7. The TGA thermograms of DPH and DPH/poly(glutamic acid) complexes (DPH/PGA).

pH-induced α-helix formation in poly(glutamic acid) is a reversible process, it is expected that solution pH increase caused α-helix collapse of poly(glutamic acid) may be associated with DPH/poly(glutamic acid) dissociation. We studied pH-induced DPH/poly(glutamic acid) dissociation by re-suspending precipitated DPH/poly(glutamic acid) into buffers of various pHs and monitor the dissolution kinetics of DPH/poly(glutamic acid) complexes for up to 7 h at 25 °C. As shown in Fig. 8, DPH/poly(glutamic acid) complexes are stable in the range of pH 2.0–4.5, even though partial dissolution of DPH/poly(glutamic acid) can be observed at pH 4.5. On the contrary, DPH/poly(glutamic acid) complexes are unstable under neutral or weak acidic conditions (pH 5–7) and DPH/poly(glutamic acid) complexes dissolve rapidly and completely. More than 95% of DPH is released from DPH/poly(glutamic acid) complexes within 20 min at neutral pH (pH 7.2). There is a close correlation between DPH/poly(glutamic acid) dissolution and poly(glutamic acid) conformation transition, from α-helix to random coil (Figs. 3b and 8), suggesting that the α-helical structure collapse of poly(glutamic acid) is responsible for pH-induced DPH/poly(glutamic acid) complex dissolution. Based on the results from dissolution experiments and TGA assay, we estimate that DPH accounts for 22% (18–26%) of the total weight of DPH/poly(glutamic acid) complexes. This pH-controlled DPH/poly(glutamic acid) complex dissolution holds the promise to yield great advances in controlled DPH release.

3.4. Taste masking test

Many active pharmaceutical ingredients (APIs) have an unpleasant taste, often very bitter. Therefore, making orally administrated drugs palatable is one of the most significant technical obstacles to "patient friendly" formulations [16,17]. Humans taste sensation occurs when molecules present in the mouth and cause neurological signals that are sent to the brain, where a taste sensation is perceived. The taste transduction is mediated by specialized neuroepithelial cells which are organized into groups of 40–100 cells and form taste buds [14,15]. Taste buds are ovoid structures, the vast majority of which are embedded within the epithelium of the tongue. Different taste modalities appear to function by different mechanisms. Since the taste is proportional to the concentration of APIs in the solution [18], prevention of API dissociation in mouth or contact with taste buds should be an effective and economic approach to taste masking. Methods used for such a purpose include polymer coating [14,19,20], solubility imitating [21], inclusion complex formation with cyclodextrin [22], liposome encapsulation [23], multiple emulsions [24], and the use of ion-exchange resins [25,26].

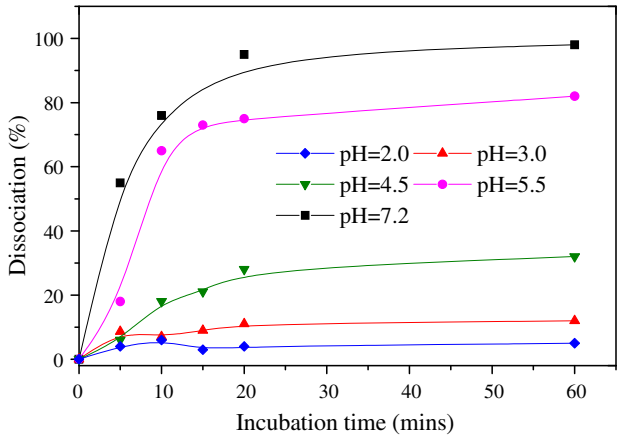

Fig. 8. The DPH/poly(glutamic acid) complex dissolution kinetics. Prepared DPH/poly(glutamic acid) complexes were suspended in 20 mM NaPB solution of various pHs. The release of free DPH from DPH/poly(glutamic acid) complexes was monitored and plotted against the incubation time.

DPH is a very bitter tasting drug. The human taste detection threshold level of DPH is of the order of 10^{-4} M. We tested the DPH taste masking effect of poly(glutamic acid) using E-tongue. Using 1.0 mg/ml of DPH solutions (equivalent to 3.43×10^{-3} M), the E-tongue is capable of distinguishing the taste profile of the addition of various sweeteners and complexes. The distance between a pair of data cluster from free DPH and formulated DPH was determined and used to assess the similarity of two samples. Sweetener sucralose was used as a taste masking control in our experiments. As shown in Table 2, the group distances of DPH/sucralose solution and DPH/poly(glutamic acid) complexes to free DPH are 1217 and 942, respectively, suggesting that poly(glutamic acid) formulation may have the comparable taste masking efficiency to sucralose when used at the tested concentration.

Currently, a large amount of sucrose or very potent sweeteners such as saccharin and sucralose are being used for diphenhydramine taste masking. Although sweeteners are the most popular taste masking excipients, intense sweeteners may be inappropriate for or cannot be accepted by certain groups of populations due to cultural differences or a disease status. Consequently, this makes the alternative taste masking strategies like that demonstrated in this study is very attractive. In practice, DPH/poly(glutamic acid) complexes can be formulated with acidic additives such as juices or sodium citrate to form either liquid or solid dosage forms for oral administration. Formulated diphenhydramines should stay in the complex form until they get to gastrointestinal tract and encounter the basic environment there. The similar pH-controlled drug release in gastrointestinal tract has been explored in oral drug delivery [27,28].

Table 2
The Electronic tongue results of various DPH complexes

	DPH/PGA	DPH/sucralose
Group distance to free DPH	942 ± 87	1217 ± 75

*DPH concentration: 1.0 mg/ml; sucralose concentration: 1.0 mg/ml. Results were presented as X ± SD, $n = 4$.

4. Conclusions

The most significance of this study is the demonstration that DPH can interact with α-helical poly(glutamic acid) specifically to form stable complexes. Since both the stability and the dissolution kinetics of formed drug/peptide complexes are tunable by adjusting both the sequences and the secondary structures of peptides, in addition to greatly expanded ion-pairing excipient pool, the advantage of using peptides as excipients is that it may solve the selectivity and stability problems faced by ion-pairing formulation. Because of the biodegradable and biocompatible natures of peptides, the peptide formulation approach demonstrated in this study holds promise to yield great advances in wide pharmaceutical applications including drug delivery, taste masking, and enhancement of drug stability.

Acknowledgements

We thank Dr. Dilhan, M. Kalyon, and Dr. Matthew Libera for their help in X-ray, DSC, and SEM experiments.

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