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International Journal of Pharmaceutics 304 (2005) 220–230
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Pharmaceutical Nanotechnology

Ibuprofen-loaded nanoparticles prepared by a co-precipitation method and their release properties

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Received 24 April 2005; received in revised form 26 July 2005; accepted 5 August 2005
Available online 22 September 2005

Abstract

A co-precipitation method was established to fabricate nano-scale core-shell particles, by which poor water-soluble drugs can be effectively dispersed with rather good stability during storage. Exemplified with formation of ibuprofen (Ib) nanoparticles stabilized by DEAE dextran (Ddex), the process includes precipitation of Ib in a supersaturated solution and deposition of Ddex onto the precipitated Ib particles through electrostatic interaction. Characterized by transmission electron microscopy (TEM), atomic force microscopy (AFM), dynamic light scattering (DLS) and zeta potential, the core-shell structure of the particles formed at pH 6.0 with a Ddex/Ib weight ratio of 5:1 was identified with Ib being the core and Ddex being the shell. As a comparison, particles formed at other pH values and other Ddex/Ib ratios were also studied. Along with increase of the Ddex/Ib ratio or pH value of the final aqueous solution, the particle size was decreased, demonstrating that the particle sizes could be readily tuned by variation of the fabrication parameters. At conditions that the Ib concentration was lower than its supersaturated value, for example at higher pH value, instead of co-precipitation mechanism, forces such as electrostatic complexation dominate the formation of Ddex-Ib particles. Moreover, drug entrapment was mainly dependent on the Ib solubility regardless of the ratio between Ddex and Ib, while the drug content was decreased as a function of Ddex/Ib ratio. In vitro release studies showed that the loaded Ib could be again released in a burst manner during the initial stage, followed with a slow rate. The final released amount of Ib showed a positive correlation with the bulk pH value, e.g. approximately 60, 80 and 90% of the loaded Ib were released in pH 1.0, 5.8 and 7.4 buffered solutions after incubation for 40 h, respectively.

Keywords: Ibuprofen; Nanoparticles; Co-precipitation; Drug release; Core-shell structure

1. Introduction

In the past decades polymeric nanoparticles have received increasing scientific and industrial interests because of their potential site-specific drug delivery to optimize drug therapy (Kreuter, 1994). Some meth-

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doi:10.1016/j.ijpharm.2005.08.008

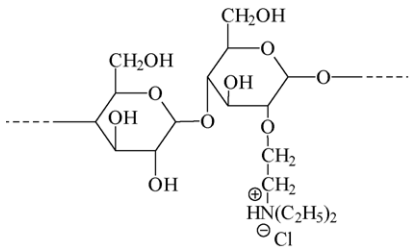
ods for fabricating nanoparticles from biodegradable polymers have been reported, including solvent evaporation (Niwa et al., 1993), monomer emulsion polymerization (Couvreur et al., 1979), salting out procedure (Allemann et al., 1993b), nanoprecipitation (Fessi et al., 1989) and complex coacervation (Bungenberg de Jong, 1949). Complex coacervation is a phase separation process that spontaneously occurs when two oppositely charged polyelectrolytes are mixed in an aqueous solution. Compared to other methods, this process can be performed entirely in an aqueous solution and at low temperature, thus has larger chance to preserve activity of the encapsulated substances. The colloidal particles produced are in the scale of nanometer or micrometer depending on the substrates or the process used, such as pH, ionic strength and polyelectrolyte concentrations (Kaibara et al., 2000; Li et al., 2002; Sanchez and Renard, 2002; Ducel et al., 2004). The major drawback of this technique is that complex coacervates have low drug loading efficiency and poor stability. Therefore, crosslinking of the complex by chemical reagents such as toxic glutaraldehyde is necessary. A pathway that can sufficiently overcome the drawback while preserve the merits of the complex coacervation is highly appreciated for safe and stable drug delivery.

We introduce here a modified complex coacervation method, named co-precipitation, by which drug loaded nanoparticles can be successfully fabricated. Lipid and bovine serum albumin has been adopted as coating layer in our previous work to disperse water-insoluble bone morphologenetic protein (BMP) in water in a form of fine particles (Jiang et al., 2004). Yet the formation mechanism of this method and the release capability of the loaded substances are not clear. We thus choose here positively charged and water-soluble DEAE-dextran (Ddex) (Scheme 1) as a coating layer to co-precipitate with negatively charged drug, exemplified with ibuprofen (Ib) to form nanoparticles at suitable pH simultaneously. The solubility of Ib is increased as a function of bulk pH, because it is highly charged and decharged at alkaline and acidic conditions, respectively. The nanoparticles fabricated by this pathway have different topology as that of the traditional aggregates or complexes formed by electrostatic interaction between the charged polyelectrolytes and the drugs. They are initially originated from the precipitates of the drugs and subsequently stabilized by the charged polysaccharides, thus have a core-shell structure. As will be demonstrated in the text, these nanoparticles contain rather high amount of drugs and have good stability during storage. Based on this interaction, the formation mechanism of the nanoparticles by the co-precipitation is suggested. Influence of fabrication conditions, particularly pH value on the particle morphology and stability are elucidated. Since Ib is a widely used drug for anti-ache and antipyretic, the resultant nanoparticles may also find some practical applications in the future. It is worth noting that the method can be extended to other drug/polyelectrolyte systems too, if the solubility of the drugs is pH-dependent.

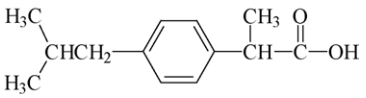
2. Experiments

2.1. Materials

DEAE-dextran (Ddex, $M_w \sim 500{,}000$) is a commercial product of Sigma. Ibuprofen (Ib) was purchased from Xinhua Pharma Chemical Co. Ltd. (Huangyan,



DEAE Dextran
(Ddex)



Ibuprofen (Ib)

Scheme 1. Molecular structure of DEAE dextran and ibuprofen.

China). All other chemicals were of analytical grade and used as received.

2.2. Preparation of Ib-loaded Ddex nanoparticles

The nanoparticles were prepared by the 'co-precipitation method' (Jiang et al., 2004). In a typical fabrication process, 40 mg Ddex and 8 mg Ib were homogeneously dissolved in 2 ml NaOH aqueous solution (pH 13). Then 0.1 M HCl was added dropwise into the above solution with interval shaking until pH of the solution reached a desired value. The solution was diluted to an extent that the concentration of Ib was 1 mg/ml by addition of a phosphate buffered saline (PBS) with the same pH value. The weight ratio between Ddex and Ib was varied from 2:1 to 7:1 and the final pH value of the solution was set from 12.0 to 6.0.

2.3. Quantification of unincorporated free Ib

After separated the nanoparticles using a membrane filtration apparatus equipped with a cellulose membrane having a pore size of 50 nm, Ib concentration of the filtered solution was characterized by UV spectroscopy taking the maximum absorbance at 221 nm. The mass of free drug was calculated by referring to a calibration curve recorded at the same conditions.

2.4. Determination of drug incorporation efficiency

Drug incorporation efficiency was expressed as drug content (%) and drug entrapment (%), which is represented by Eqs. (1) and (2), respectively (Govender et al., 1999). The mass of the nanoparticles was calculated from the difference between weight of the raw materials and the dried substances in the filtered solution. Each value was averaged from three parallel measurements and expressed as mean ± standard deviation.

$$\text{Drug content (\%, wt/wt)} = \frac{(\text{mass of the total drug} - \text{mass of free drug}) \times 100}{\text{mass of nanoparticles}} \quad (1)$$

$$\text{Drug entrapment (\%, wt/wt)} = \frac{(\text{mass of the total drug} - \text{mass of free drug}) \times 100}{\text{mass of total drug}} \quad (2)$$

2.5. In vitro Ib release

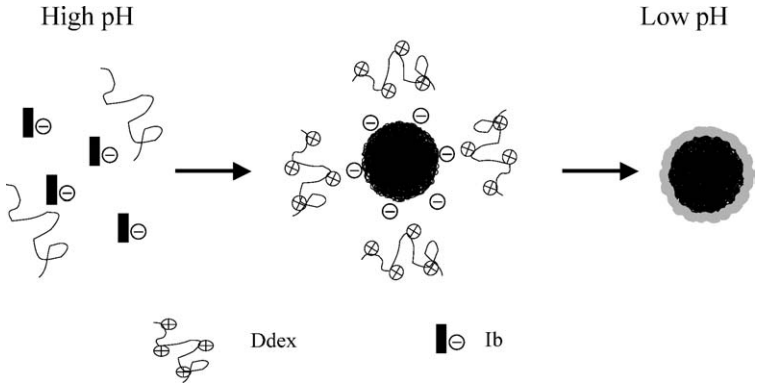
The in vitro Ib release behavior from the nanoparticles was determined using a dialysis technique. Three millilitre particle solution was filtered to remove its solvent. Then 3 ml PBS solution with the same pH value was added to disperse the particles. The resultant dispersion was introduced into a sealed filter membrane with a cut-off molecular weight of 10,000 Da. The sealed membrane was immersed into 40 ml PBS solution with a given pH value at 37 °C. At each time interval, 4 ml released medium was taken out for UV measurement as described above. The total leaching solution was maintained at 40 ml by addition of 4 ml fresh PBS solution. Free Ib was also put into the same filter membrane as a control.

2.6. Characterizations

The particles were loaded on a 200 mesh copper grid and observed under a transmission electron microscope (TEM, JEM 200CX) at 100 kV electron beam accelerating voltage. For atomic force microscopy (AFM) observation, 10 μl particle solution was dropped onto freshly cleaved mica. After dried at room temperature, images were taken by AFM (SPI3800N, Seiko) adopting a scanning force mode. Nanoparticle size and zeta potential were determined using dynamic light scattering (DLS, Zetasizer 2000). The particle size analysis was performed at a scattering angle of 90° at room temperature. The concentration of the particles was adjusted to an appropriate value by pure water filtered through a 0.22 μm membrane. The diameter was averaged from three parallel measurements and expressed as mean ± standard deviation.

3. Results and discussion

To demonstrate the idea of co-precipitation in fabrication of nanoparticles, we shall present first the



Scheme 2. Schematic illustration to show the formation process and the structure of ibuprofen/Ddex core-shell particles.

basic formation mechanism. Ddex nanoparticles incorporated with Ib are then fabricated and characterized accordingly. Finally, effects of Ddex/Ib ratio and pH of final solution on the nanoparticles size, drug loading capacity and drug release properties will be elucidated.

3.1. Fabrication of Ib loaded nanoparticles based on co-precipitation

A schematic presentation to illustrate the forming process and the possible mechanism of the co-precipitation method is given in Scheme 2. At high pH such as in a 0.1 M NaOH solution, ibuprofen is deprotonated with high solubility (Table 1) (Hadgraft and Valenta, 2000). Due to the existence of carboxylate group, it should be negatively charged. In this solution the soluble Ddex is roughly uncharged. Along with decrease of the pH value, Ib will become less soluble and Ddex will gain net positive charge gradually. When the pH is lower than a critical value, Ib is supersaturated and thus precipitation will occur. In the presence of Ddex, the initially formed Ib tiny particles will be simultaneously covered by the polysaccharides via electrostatic interaction. These hydrophilic and charged molecules in the shell layer will then retard further accumulation between the particles through hydrostatic and charge repulsion forces. In this case formation of stable nanoparticles can be expected with a core-shell structure. Since the process includes precipitation of the core materials followed by deposition of the shell layers, it is called ‘co-precipitation’ for brevity.

Table 1
The solubility of ibuprofen as a function of pH

pH	1.0	6.0	7.0	9.0	12
Solubility (mg/ml)	0.02	0.23	1.46	7.54	31.53

To demonstrate the applicability of this method, two pH values of the final solutions were compared taking the Ddex/Ib ratio of 5:1 (Fig. 1). When the pH of the final solution was set at 9.0, particles could be formed as detected by both AFM and TEM characterizations. The particles have sizes varied from several nanometers to decades nanometers with spherical shape observed under AFM (Fig. 1a). TEM illustrated a very loose and fluffy particle structure (Fig. 1b and c). This would mean that at this pH value, the Ib and Ddex cannot be perfectly coacervated to form compact particles. Since the concentration of Ib was 1 mg/ml which is far below the critical solubility of 7.54 mg/ml (Table 1), the particles should thus be formed through simple complexation between Ib and Ddex by electrostatic interaction instead of co-precipitation.

When the pH of the final solution was set at 6.0, the concentration of Ib (1 mg/ml) was already larger than its solubility (0.23 mg/ml). Consequently, precipitation of Ib would then occur spontaneously. At this case, compact particles with quite homogenously size distribution were obtained (Fig. 1d–f). Measured from AFM (Fig. 1d) and TEM (Fig. 1e), the particle size was increased to approximately 120 nm. The magnified TEM image (Fig. 1f) shows unambiguously that the particle possesses a core-shell structure, in which the compact dark core is surrounded by a light gray shell presumably made of Ddex. The thickness of the shell layer is about 20 nanometers. The particles exhibit

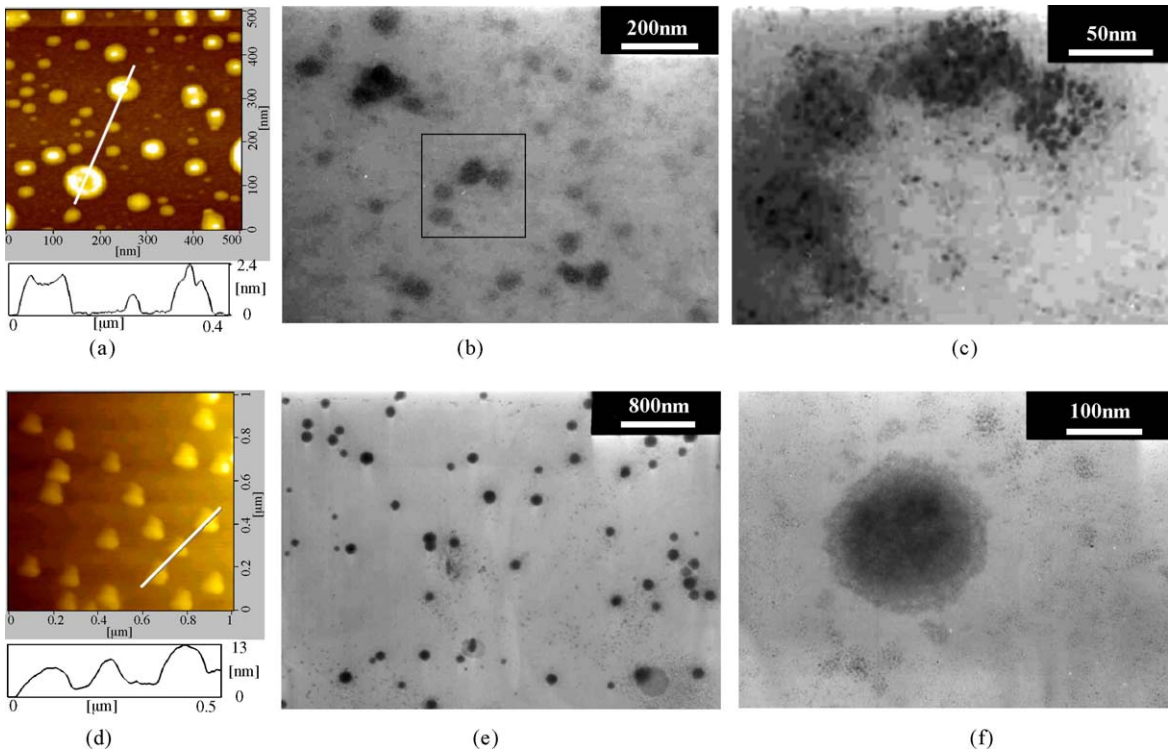


Fig. 1. AFM (a and d) and TEM (b, c, e and f) images to show particles fabricated at a Ddex/Ib ratio of 5:1 in pH 9.0 (a–c) and in pH 6.0 solutions (d–f). The plots below the AFM images (a and d) are line profiles recorded at positions shown in (a) and (d), respectively.

a ζ-potential of 13.0 ± 0.5 mV, which is equal to the value of Ddex (13.5 ± 1.7 mV). Since ζ-potential of colloidal particles is decided primarily by their surface properties, this result indicates that the particle surfaces should be surely composed of Ddex. Of course the existence of Ddex/Ib complex in the shell layer cannot be fully ruled out. The interior cores of the particles are considered as Ib, which is accordance with the fact that more than 77% of Ib should be insoluble and precipitate from the solution. The core-shell structure and positive-charged surface of the particles have also provided conceivable evidence for the above formation mechanism of co-precipitation.

Fixed the pH value at 6.0 of the final solution, the influence of Ddex/Ib ratio on morphology of the formed particles was further investigated. As can be known from the mechanism, sufficient amount of Ddex is required to form stable particles. Insufficient Ddex would cause instability and coalescence of particles as illustrated here at Ddex/Ib ratio of 2:1 (Fig. 2). The particles had a comparatively uniform size of ~200 nm and homogeneous structure like skined oranges (Fig. 2a). Each particle was most likely a cluster of several smaller ones (Fig. 2b). TEM characterization displays still the core-shell structure except for more loosely compact core structure (Fig. 2c). The existed nanopores as indicated by the arrow is understood as the result of cavities in-between the accumulated tiny particles. When the Ddex/Ib ratio was set at 7:1, particles with size of ~100 nm and similar morphology as that of 5:1 were obtained. They showed also compact core structure and well dispersed property.

3.2. *Effect of solution pH and Ddex/Ib ratio on ζ-potential and particle size*

To explore the influence of preparation conditions on the particle properties, a systematical study was performed by variation of solution pH and Ddex/Ib ratio. Since particle size is one of the most important parameters in drug carriers for intravascular delivery (Qiu et al., 2001), we thus concern here mainly the parti-

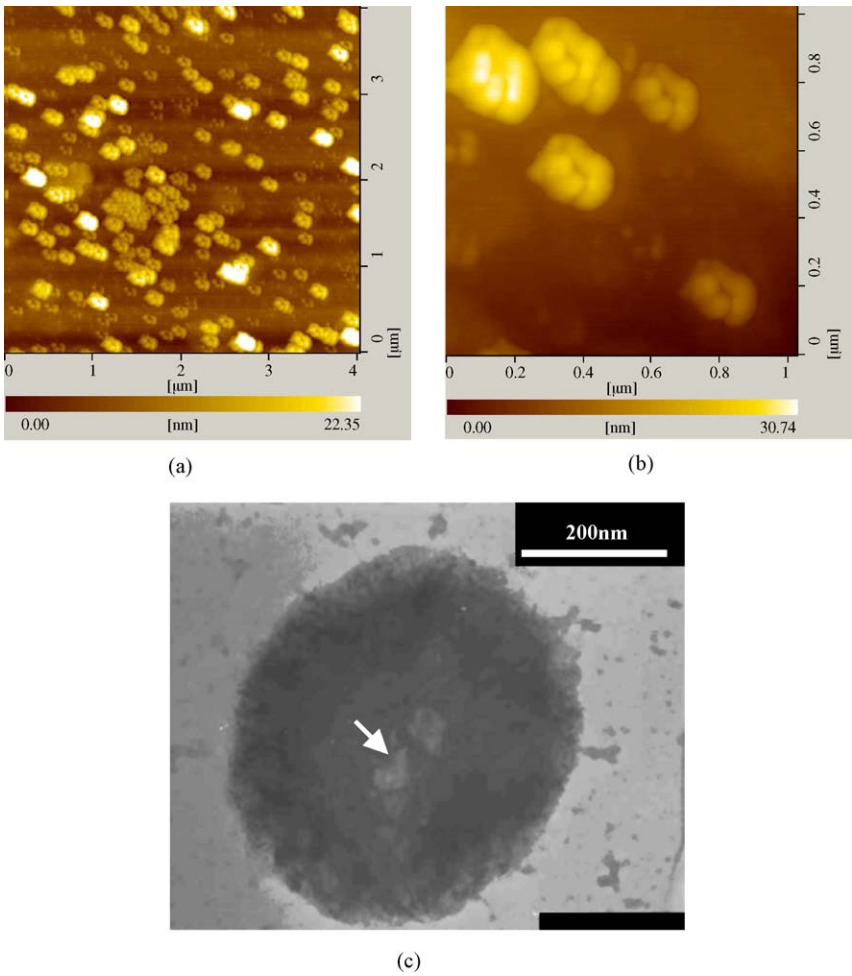


Fig. 2. AFM (a and b) and TEM (c) images to show particles fabricated in pH 6.0 solution at a Ddex/Ib ratio of 2:1, (b) is a higher magnification of (a).

cle size and surface charge which are monitored by dynamic light scattering (DLS). As mentioned above, the solution pH dramatically influences ionization of both Ib and Ddex, and the solubility of Ib. This will of course change the electrostatic interaction and precipitation behavior of Ib which in turn decide the resultant particle size and structure. Fig. 3 displays that the hydrodynamic diameter of the particles increased slowly along with decrease of the pH value, while the ζ-potential of the particles increased almost linearly from 5.5 ± 0.3 mV at pH 12 to 13.0 ± 0.5 mV at pH 6.0. A sudden increase of the particle size took place from pH 7.0 to pH 6.0. This growth behavior of the particle size is closely associated with the solubility of Ib (Table 1). Since the concentration of Ib used here is 1 mg/ml, above pH 7.0 all the Ib is preferable in a highly soluble state except for complexation with Ddex. Therefore, only slight increase of size is recorded, which should be largely caused by the enhanced complexation ability at relatively lower pH value as evidenced by the ζ-potential results. Actually, the average particle size (12.7 nm) in a pH 12.0 solution is very close to that of pure Ddex (9.6 nm). After the pH value is decreased to 6.0, co-precipitation occurs to yield larger particles. At still lower pH such as 5.0, macroscopic detectable needle-like precipitate was found in the solution, demonstrating Ib microcrystals of larger size have been formed.

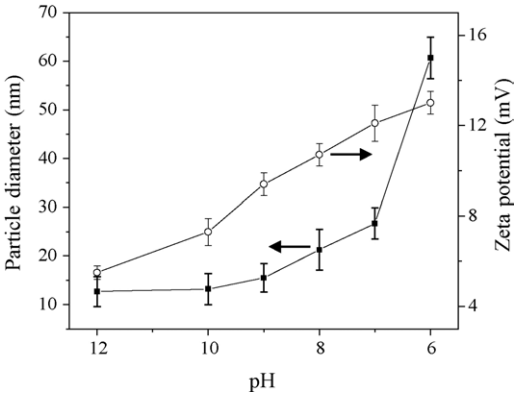


Fig. 3. Particle size and zeta potential as a function of solution pH. The ratio between Ddex/Ib was fixed at 5:1. Each datum was averaged from three parallel measurements.

The aggregation behavior of the initially formed particles is basically controlled by the cover layer, i.e. Ddex, which in turn affects the final particle size (De and Robinson, 2003). Fixed the pH value of the final solution at 6.0 and 9.0, respectively, the influence of Ddex/Ib ratio on the particle size and the ζ-potential was monitored as shown in Fig. 4. The particle diameter formed at pH 6.0 solution was decreased sharply from 210 to 90 nm when the Ddex/Ib ratio was changed from 2:1 to 3:1. A further increase of the Ddex/Ib ratio caused again decrease of the particle size, but in a very minimal scale. Contrast to the nonlinear change manner of the particle size, the ζ-potential was increased almost linearly as a function of the Ddex/Ib ratio. At the Ddex/Ib mass ratio of 2:1 and 3:1, the ζ-potentials of the particles were much lower than that of pure Ddex (13.5 ± 1.7 mV). This would mean that Ib might have been partly involved into the Ddex shell layer because of relatively insufficient Ddex at these conditions. As a result of the weak electrostatic interaction, particle aggregation would then result in larger particles (see also Fig. 2a and b) so that the surface energy could be reduced. When the Ddex/Ib ratio was improved to 5:1, the particles had a same ζ-potential as pure Ddex, indicating that Ib was scarcely involved into the Ddex shell layer. Together with the effect of pH value, one can then conclude that a proper Ddex/Ib ratio (e.g. 5:1) and pH value (for example, 6.0) should be adopted to obtain the nanoparticles with smaller size and higher stability. By comparison, the particle diameters formed at pH 9.0 at all the Ddex/Ib ratios were much smaller than that

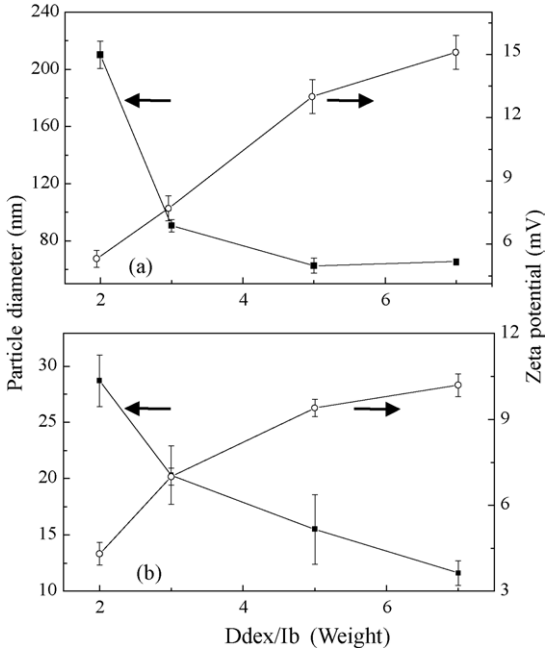


Fig. 4. Particle size and zeta potential fabricated in (a) pH 6.0 and (b) pH 9.0 solutions as a function of Ddex/Ib ratio. Each datum was averaged from three parallel measurements.

obtained at pH 6.0. They were deceased slightly from 28.7 to 11.6 nm when the Ddex/Ib ratio was changed from 2:1 to 7:1 (Fig. 4b). Again, the ζ-potential was increased almost linearly (Fig. 4b) as that at pH 6.0. When the Ddex/Ib ratio was improved to 5:1, the particles had a same ζ-potential as that of pure Ddex (10.7 ± 0.8 mV).

3.3. Effect of Ib/Ddex ratio and pH on drug entrapment

Measured by UV spectroscopy, the drug entrapment (denoting the loading efficiency of Ib) and the drug content (denoting the percentage of Ib in the nanoparticles) are summarized in Table 2. The data show that the drug entrapment is approximately 70% regardless of the Ddex/Ib ratio and the particle size at pH 6.0. This value is quite close to the precipitate percentage of Ib from the solution, which is 77% [(1 mg/ml − 0.23 mg/ml)/(1 mg/ml)] (for solubility, see Table 1). This conveys a hint that the entrapment of Ib at pH 6.0 should be surely driven by the co-precipitation. With the increase of Ddex, more

Table 2
Drug entrapment and drug content of Ib-Ddex nanoparticles prepared in a pH 6.0 or 9.0 buffered solution

Ddex/Ib (w/w)		Drug entrapment (% w/w)	Drug content (% w/w)
pH 6.0	2:1	72.2 ± 1.5	31.6 ± 1.8
	3:1	71.7 ± 2.1	21.8 ± 0.9
	5:1	72.0 ± 0.9	13.6 ± 1.4
	7:1	70.1 ± 1.4	9.6 ± 0.6
pH 9.0	2:1	57.0 ± 1.1	23.5 ± 0.9
	3:1	56.4 ± 0.6	16.6 ± 0.8
	5:1	57.6 ± 0.4	10.6 ± 0.4
	7:1	57.5 ± 1.0	7.7 ± 1.3

Ddex will be incorporated into the nanoparticles. As a result, the relative drug content in the nanoparticles was decreased from 31.6 to 9.6% (w/w) when the Ddex/Ib ratio was increased from 2:1 to 7:1 (Table 2).

As a comparison, the drug entrapment and the drug content were also quantified when the final pH was set at 9.0. Again the drug entrapment is almost a constant regardless of the feeding ratio of Ddex/Ib, but the value is decreased to approximately 57%. Moreover, the drug content was decreased accordingly. By referring to Table 1, it can be known that incorporation of Ib in this case is more likely driven by complexation between the oppositely charged Ddex and Ib, since Ib is completely soluble at pH 9.0. The reason why a constant drug entrapment of Ib is not well clear at present. One possible explanation could be that only those strongly complexed Ib molecules are remained after filtration, while those loosely attached ones are released. The ratio between the strongly and the loosely attached Ib molecules might be decided mainly by the nature of the Ib (such as inter molecular interaction

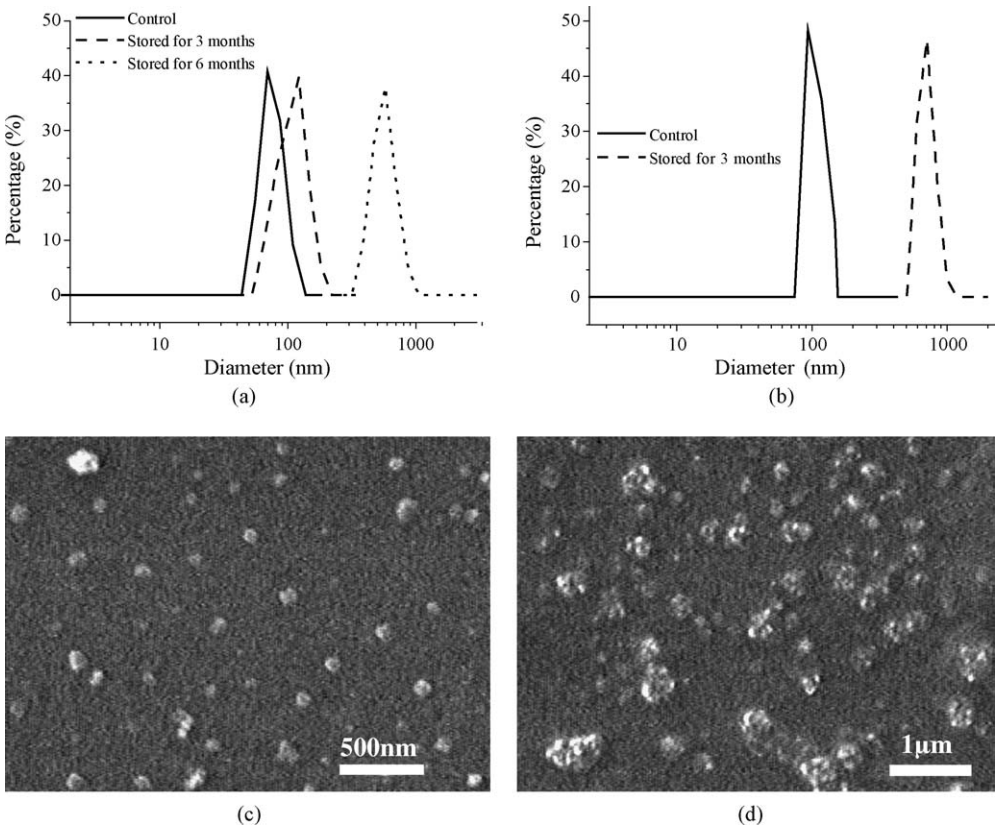


Fig. 5. Alteration of size and size distribution of Ib/Ddex nanoparticles after stored at 25 °C for different time. Particles were fabricated in pH 6.0 solutions with a Ddex/Ib ratio of 5:1 (a) and 2:1 (b), respectively. SEM images of particles (a) that are of the control (c) and that stored for 6 months (d).

and J-aggregation, etc.), which could then result in the same drug entrapment.

3.4. Stability during storage

Coagulation between the particles during storage will dramatically influence the performance of the Ib-loaded particles. Monitored by DLS, different particle growth behaviors were revealed as shown in Fig. 5. For particles fabricated at pH 6.0 with a Ddex/Ib ratio of 5:1 (Fig. 5a), they present only a slight increase of their average size and broadening of their size distribution after stored for 3 months. No substantial loss of Ib was detected at this time. Significant coagulation of the particles was detected after stored for 6 months, as evidenced by the fact that the particles have increased their size from 60 to 600 nm with a broad size distribution (Fig. 5a). This was further confirmed intuitionally by SEM observations. Compared with the initially fabricated nanoparticles (Fig. 5c), particle clusters are observed after stored for 6 months (Fig. 5d). However, severe particle coagulation had already been observed after stored for 3 months for particles fabricated at the same pH value but with a smaller Ddex/Ib ratio (2:1) (Fig. 5b) or at the same Ddex/Ib ratio but at higher pH value (pH 9.0). The ζ-potential of the particles fabricated at pH 6.0 with a Ddex/Ib ratio of 5:1 and 2:1 decreased slightly from 13.0 ± 0.5 mV to 10.7 ± 0.3 mV and from 5.3 ± 0.4 mV to 3.3 ± 0.5 mV after stored for 3 months, respectively. While the ζ-potential of the particles fabricated at pH 9.0 with the same Ddex/Ib ratio decreased dramatically from 9.4 ± 0.5 mV to -1.7 ± 0.8 mV, implying that the particles had almost lost their surface charge completely. A reasonable explanation for ζ-potential change could be that the free Ib (either originally existed or released afterwards) may adsorb onto the particle surface gradually, leading to neutralization of the surface charge. Because of larger solubility and stronger negative charge of Ib at higher pH, it will have larger chance and stronger ability to combine with Ddex. This weakening or even neutralization of the surface charge will then cause the coagulation of the particles. The above results demonstrate that the particles fabricated at pH 6.0 with Ddex/Ib ratio of 5:1 have better stability against coagulation during storage, and thus are subjected for further release study in vitro.

3.5. In vitro drug release

While the Ddex/Ib nanoparticles have been successfully fabricated, the question arises whether the loaded Ib can be released afterwards. As the solubility of Ib is pH-dependent (Table 1), which in turn influences the drug release rate and final release amount (Qiu et al., 2001), we thus chose three pH values for Ib release from nanoparticles fabricated at Ddex/Ib ratio of 5:1 and at pH 6.0. Fig. 6 shows that a burst release behavior was recorded at the initial stage (within 2 h) regardless of the pH values of the buffered solutions. This is very similar to that of the control Ib crystals without Ddex covering layer (released at pH 7.4), except for that Ib of the control released completely within ~2 h with a much faster rate. After the burst release, the Ib-loaded particles showed continuous slow release profiles till the longest time measured so far (40 h), especially for those incubated in solutions having pH values of 5.8 and 7.4. For Ib-loaded particles released in pH 1.0, 5.8 and 7.4 solutions, the final released percentage at 40 h are approximately 60, 80 and 90%, respectively. These preliminary results have roughly demonstrated that diffusion of the Ib molecules from the particle cores to the bulk solution is surely retarded by the Ddex shell layers. The comparatively lower released amount at pH 1.0 should be attributed to the lower solubility. At this

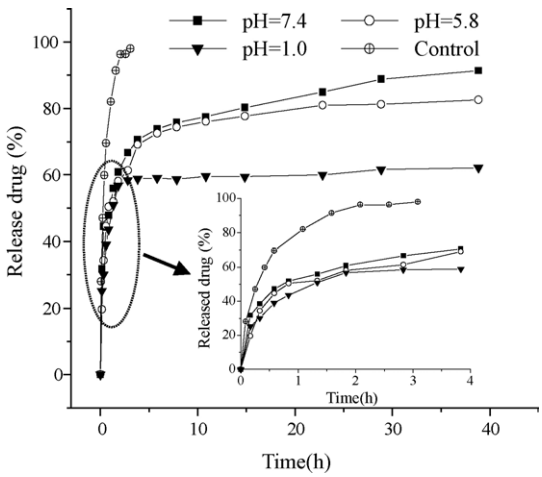


Fig. 6. Release profiles of Ib from particles in buffered solutions with different pH values. The particles were fabricated in a pH 6.0 solution with a Ddex/Ib ratio of 5:1. Bare Ib crystals were used as control sample whose release was conduced in a buffered solution with a pH value of 7.4.

pH condition a final concentration of 0.016 mg/ml was measured, which should be rather close to the saturated value by referring to Table 1 (noting that the pKa of Ib is 5.2–5.6 (Hadgraft and Valenta, 2000). Below this pH value, the solubility changes very minimal). At pH conditions of 5.8 and 7.4, however, the incomplete release should be caused mainly by the electrostatic association between the Ddex and Ib molecules, since the final concentrations of Ib should be far less than that of their corresponding saturated values. The burst release at the initial stage, a quite normal phenomenon in many drug release systems (Leo et al., 2000) should be ascribed to rapid dissolution of Ib since a larger amount of fresh buffered solution is added. This has in fact conveyed a hint that the retarding effect of the Ddex layer is quite limited.

4. Conclusions

Nano-scale ibuprofen particles covered with DEAE dextran have been successfully fabricated by a co-precipitation method. Results obtained from TEM, AFM, DLS, ζ-potential and solubility demonstrated both the core-shell structure of the particles and the co-precipitation mechanism. The process of particle formation can thus be verified, which includes the precipitation of ibuprofen in a supersaturated solution created by pH decrease and deposition of the positively charged Ddex onto the precipitated particle surfaces. The morphology, size, drug entrapment, drug content and release behavior of the nanoparticles were all affected by the fabrication parameters and environmental conditions such as Ddex/Ib ratio and the solution pH. Example was given to show that typical core-shell particles could be obtained by the co-precipitation mechanism in a pH 6.0 solution at a Ddex/Ib ratio of 5:1. At conditions that the Ib concentration was lower than its supersaturated value, nanoparticles could be formed as well, which is mainly driven by electrostatic complexation between the oppositely charged Ib and Ddex. All these results demonstrate that by this method Ib loaded nanoparticles can be spontaneously obtained under very mild conditions without involving high temperatures, organic solvent or/and sonication. The particles are positively charged and the loaded Ib can be released afterwards. Since Ddex has been widely used as a major component for cell carriers (Cytodex 1), it can be predicted that the Ddex/Ib nanoparticles produced here should possess enough safety for biomedical use.

Acknowledgments

This study is financially supported by the Natural Science Foundation of China (nos. 20434030 and 90206006) and the National Science Fund for Distinguished Young Scholars of China (no. 50425311).

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