Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 253 (2003) 145–157
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Use of coated microtubular halloysite for the sustained release of diltiazem hydrochloride and propranolol hydrochloride

S.R. Levis, P.B. Deasy*

Department of Pharmaceutics and Pharmaceutical Technology, School of Pharmacy, Trinity College, University of Dublin, Dublin 2, Ireland

Received 11 October 2002; received in revised form 9 December 2002; accepted 11 December 2002

Abstract

Halloysite is a naturally occurring microtubular aluminosilicate mineral. The highly water soluble cationic drug, diltiazem HCl, was shown to bind to the polyanionic surfaces of the material to achieve a slight sustained release effect on dissolution testing due to reversible chemisorption and/or hindered release from the drug loaded lumen. A greater sustained release effect was more apparent when the less water soluble cationic drug, propranolol HCl, was examined. Attempts to further delay drug release by loading diltiazem HCl from a polyvinylpyrrolidone solution into the halloysite had little effect. However, a range of cationic polymers, including chitosan cross-linked with glutaraldehyde, was shown to bind to halloysite and was used to achieve significant delayed drug release. Coating with adequate polyethyleneimine was particularly effective at delaying drug release, being dependent on the architecture of the interaction between the polycation and the mineral. When a range of alkyl-2-cyanoacrylate monomers applied from a non-aqueous solvent by an in situ polymerisation procedure was examined, diltiazem HCl loaded halloysite dispersed in poly-*iso*-butyl cyanoacrylate was found to be the most effective at reducing the burst effect noted with aqueous coating systems.

Keywords: Halloysite; Microtubular; Sustained release; Diltiazem HCl; Propranolol HCl

1. Introduction

Halloysite is an unusual clay mineral, having a hollow tubular structure in the submicron range, measuring typically 3 μm long × 0.3 μm outer diameter and like most natural materials it varies somewhat in size within and between deposits. It is defined as a two-layered aluminosilicate, and is chemically similar to kaolin, which however, has a stacked plate-like structure. The extensive characterisation of this material has been described recently by us (Levis and Deasy, 2002), highlighting its potential for drug loading, particularly of cationic agents by chemisorption onto its polyanionic faces or more extensively by entrapment into its hollow lumen or core. Lipid microtubules or carbon nanotubules have similar morphology with potential for drug loading, but compared to the abundant commercial supplies of halloysite available worldwide at low cost, they are likely to remain prohibitively expensive for most pharmaceutical applications. To-date no studies dealing with the use of halloysite for sustained delivery of drugs have been published, though recently work on its use for the extended release of a range of marine biocides has appeared (Price et al., 2001).

Diltiazem HCl was chosen as the main model drug for these studies, because it is a calcium channel blocking agent, frequently administered orally for the

* Corresponding author. Tel.: +353-l-608-2784; fax: +353-l-608-2783.
E-mail address: pdeasy@tcd.ie (P.B. Deasy).

0378-5173/03/$ – see front matter
doi:10.1016/S0378-5173(02)00702-0

treatment of angina and hypertension as a sustained release product to improve clinical efficacy. Of particular relevance to this study is that the drug is also cationic facilitating surface binding to the faces of halloysite, and is highly water soluble (>50%, w/v at 25 °C as reported by Yang and Fassihi, 1997) facilitating easy drug loading into the lumen but posing a very demanding challenge to achieve adequate sustained release property due to the anticipated high diffusion gradient produced. Some comparative studies are reported also with another low molecular weight cationic drug frequently formulated as an oral sustained release product, propranolol HCl, which however, is less soluble in water (5%, w/v at 25 °C; Yang and Fassihi, 1997) and, consequently, should more easily demonstrate prolonged release from this novel microtubular material.

2. Materials and methods

2.1. Materials

A single large batch (25 kg) of halloysite, grade G, adequate for all the reported studies, was obtained from New Zealand China Clays Ltd., Auckland, New Zealand and sieved prior to use through a 125-μm mesh. Acetic acid, glutaraldehyde 25%, sodium acetate (Sigma Chemical Co., St. Louis, MO), chitosan, medium molecular weight, polyethyleneimine (PEI), 50%, molecular weight 25,000 (Aldrich), citric acid monohydrate, di-sodium hydrogen phosphate dodecahydrate (Riedel de Haen), diltiazem hydrochloride (Profarmaco), eudragit E 100 (Rohm Pharma), glucose (Merck), heptane, tetrahydrofuran (Rathburn), methanol, HPLC grade (Scharlau), nitrogen (Air Products), octyl, *n*-butyl and *iso*-butyl cyanoacrylate (Loctite), propranolol hydrochloride (Finechem) and water (glass distilled) were used. All reagents were GPR unless otherwise indicated.

2.2. Determination of halloysite/cation binding curves

The first technique employed to determine the extent of binding between the polyanionic surfaces of halloysite and the cationic polymer chitosan at appropriate pH involved viscosity measurement. Chitosan solutions 0.2% (w/v) were prepared, buffered at pH 2.8 or 4.5 using 0.1 M acetic acid or 0.1 M sodium acetate, respectively, and 20 ml volumes of these solutions were mixed with 2, 4, 6, 8, 10, 12, 14, 16, 18 or 20 ml of an aqueous halloysite suspension 0.1%, followed by dilution to 40 ml with buffer to maintain constant volume. Thus, total chitosan concentration was fixed at 0.1% in all samples, but the halloysite content varied. The sample systems were then incubated at 37 °C for 48 h in a temperature-controlled reciprocating water bath (Precision Scientific) set to shake at 50 rpm. After incubation, the samples were centrifuged (Sanyo Harrier) for 20 min at 3000 rpm and the flow time of the recovered supernatant solutions compared to the pure buffer was determined in triplicate at 37 °C using a suspended level viscometer (Ubbelhode, size 1, Technico). The specific viscosity was calculated from the mean data.

In the second technique employed, halloysite binding curves were constructed for the cationic drug diltiazem HCl and two other possible cationic coating polymers, PEI and eudragit E, using a UV analysis technique. One hundred milligram samples of halloysite were mixed with 50 ml solutions of the aqueous cationic substances (5–160 mg diltiazem HCl, 2–30 mg PEI, 2.5–80 mg for eudragit E) in 100 ml conical flasks, which were shaken at 25 °C for 20 min at 500 rpm. Samples of the supernatants were removed, filtered through 0.2 μm membrane filters (Gelman) to remove particulate material and analysed by UV (Shimadzu) at wavelength 236 nm for diltiazem HCl, 209 nm for PEI or 229 nm for eudragit E. The difference in concentration of the cation solution, based on the mean of triplicate determinations with use of an appropriate calibration curve for each substance, before and after incubation corresponded to the amount bound to the fixed weight of halloysite.

2.3. Loading of halloysite with diltiazem HCl or propranolol HCl

Samples of halloysite (1.5 g) were mixed with 1.5 ml of the drug solution (diltiazem HCl, 40%, w/v in purified water; propranolol HCl, 20%, w/v in methanol). The wetted halloysite was placed in a sealed desiccator vessel and vacuum applied (∼30 mm Hg) for 30 s until all the gas was removed. The vacuum was reapplied twice to ensure that the drug

solution had fully displaced all the air present between and within the microtubules. The drug loaded samples were then dried in a forced circulation oven (Memmert) for atleast 24 h at 50 °C to constant weight. The dried powders were removed from the oven, lightly ground down using a mortar and pestle, and sieved through a 125-μm mesh to separate any large agglomerates formed in the loading process.

2.4. Thermogravimetric analysis of dried drug loaded halloysite

Thermogravimetric analysis (TGA) was performed using a Toleda TC15 TA controller (Mettler). Analysis was performed over the temperature range 30–250 °C using a heating rate of 10 K/min. The sample weights examined were between 5 and 10 mg. Nitrogen gas flowed over the open crucibles containing the sample as the analysis was performed. The percentage weight losses incurred during the heating cycle were estimated using the associated software.

2.5. Coating drug loaded halloysite

The first coating procedure examined involved charge neutralisation, whereby appropriate quantities of the dried drug loaded halloysite powder were added to 100 ml conical flasks and 50 ml quantities of aqueous solutions of each cationic coating material, buffered as necessary, were added followed by stirring at 500 rpm for 2 min. Glutaraldehyde (10 or 20%, w/v) was added as cross-linking agent, if appropriate. The suspensions were then centrifuged at 3000 × *g* for 10 min and the coated halloysite recovered as sediment was dried in a forced circulation oven at 50 °C to constant weight, before being lightly ground to a fine powder that was passed through a 125-μm mesh.

The second coating procedure examined involved in-situ polymerisation using cyanoacrylate monomers. Samples of drug loaded halloysite (3 g) were added to 20 ml volumes of 5 or 10% solutions in heptane of octyl, *n*-butyl or *iso*-butyl cyanoacrylate in dry 100 ml conical flasks. The suspensions were allowed to stir at 500 rpm at room temperature for 30 min, 3 or 8 h, during which surface polymerisation occurred progressively, initiated mainly by residual-free water present, which was previously estimated at 9.5% (Levis and Deasy, 2002). The reaction was quenched by filtering off the encapsulated halloysite, which was dried at 50 °C to constant weight, ground and sieved as described above. Samples of the polycyanoacrylate drug loaded halloysite were washed with tetrahydrofuran to remove the coating and the molecular weight of the polymers formed was determined by gel permeation chromatography (Perkin-Elmer).

2.6. Dissolution studies

Various products were subject to dissolution testing at 37 °C in 1 l of McIlvaine's buffer, pH 6.8 or 3.2, using baskets rotated at 100 rpm and located 25 mm above the base of the vessel (model DT6, Copley). Finer products were retained in the baskets by sealing into coarse membrane filters. Samples (5 ml) were withdrawn periodically with immediate replacement of the dissolution medium, and following filtration through a 0.45-μm filter (Gelman), were assayed by UV spectroscopy (Shimadzu UV-160) at the appropriate wavelength.

Similarity factors (f_2) for comparing dissolution profiles were calculated and interpreted as described by Tang and Gan (1998), values below 50 indicating significant difference.

2.7. Electron microscopy studies

Samples of product were mounted on aluminium stubs, vacuum coated with gold film (Polaron SC 500) and examined using a scanning electron microscope (Hitachi S-4300 field emission).

3. Results and discussion

3.1. Ionic binding

The curve for diltiazem HCl binding with the anionic sites present on the outer and inner surfaces of halloysite microtubules is shown in Fig. 1. The plot is unusual in that as the amount of drug added to halloysite increases the amount bound increases initially, then decreases before increasing again to reach a plateau. The pH of all the bulk suspensions remained relatively constant at 7.17–7.43 and is unlikely to account for the unusual binding profile observed. A more likely explanation is change in the pH within

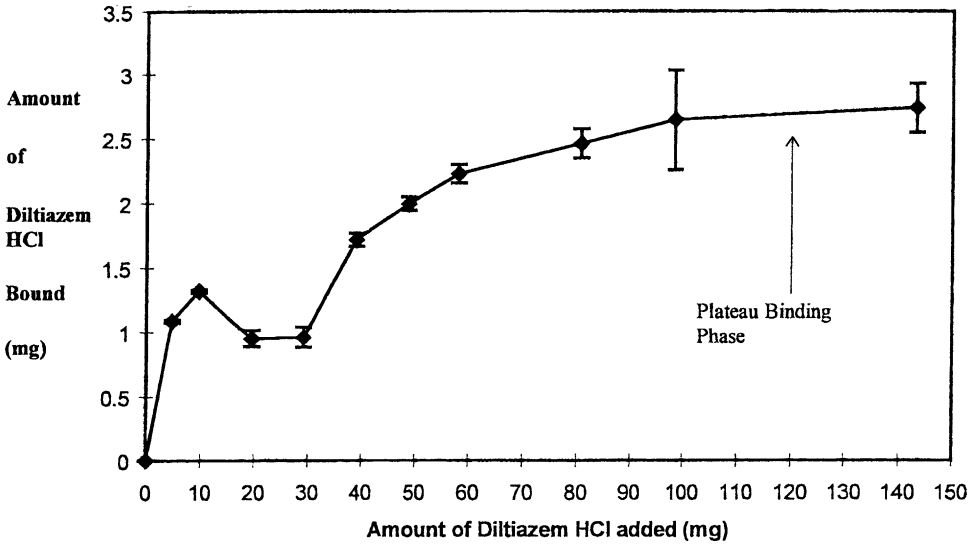

Fig. 1. Binding profile showing the effect of increasing amount of diltiazem HCl added to 100 mg halloysite in water on the level of drug bound.

the microenvironment of the halloysite surface. When low concentrations of the drug solution are added to the halloysite suspension, the pH of the mineral's surface would be relatively high (~7.4) and hence the strongly electronegative surface has a high binding affinity for the cationic drug. As more added drug locates in proximity to the halloysite surface, the accumulation of the acidic drug causes the microenvironment around the mineral to become increasingly acidic, altering the ionisation of the siloxane groups, thereby reducing the overall negative charge and hence sites available for drug binding. The second binding phase could be due to a build-up of a second adsorbed layer due to hydrophobic adsorption of unionised drug (approximately 50% as the pK_a of the drug is 7.7) to itself or to hydrophobic binding sites on the halloysite surface. Ultimately, a final plateau is reached, indicating complete saturation of all available binding sites by the drug, which was estimated from the plot to be ~2.4 mg per 100 mg halloysite.

3.2. Tubular entrapment

The potential entrapment volume was estimated previously as ~0.25 ml/g (Levis and Deasy, 2002) and, consequently, the volume of drug solution used resulting from the use of a 1:1 ratio was approximately four times the tubular volume available. It was possible to load this larger drug solution volume into the lesser tubular volume due to the fact that the low pressure created by the vacuum procedure employed tended to cause premature evaporation of the drug solvent, water, thereby effectively reducing the actual volume being loaded. This also had the advantage of concentrating the drug within the tubules to a level greater than the saturation concentration the loading solution, promoting very high loading. Using a 40% (w/v) aqueous diltiazem HCl solution at a 1:1 ratio, the theoretical entrapment of the drug was calculated to be 28.5% (w/w) of the final product, but was determined to be only 25.6% on dissolution testing in water, the discrepancy being due mainly to poorly liberated ionic bound drug (~2.4%, w/w).

The release of drug from the loaded halloysite was examined by dissolution testing in buffer media pH 3.2 and 6.8, simulating gastric and small intestinal pH conditions, as shown in Fig. 2. Release of free drug at both pHs was equally rapid and for clarity is plotted at one pH only. Diltiazem HCl release from halloysite, compared to the free drug, was only slightly retarded, with a large burst effect evident at both pH values, indicating that for a highly water soluble, low molecular weight drug, simple entrapment in halloysite is unlikely to be effective for producing adequate sustained

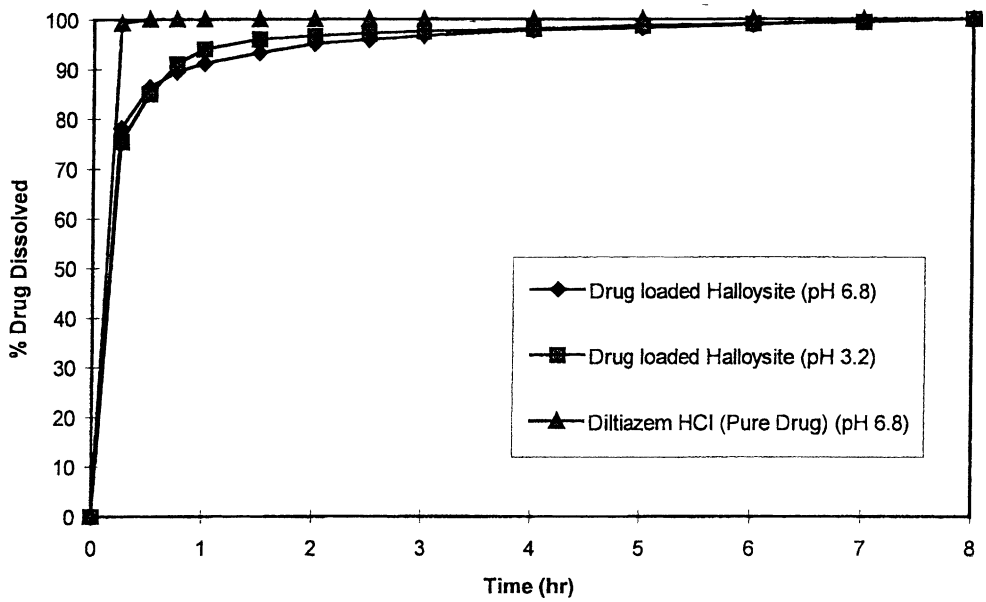

Fig. 2. Dissolution of diltiazem HCl from drug loaded halloysite at pH 3.2 and 6.8 for 8 h at 37 °C, compared to free drug at pH 6.8.

release property. This is not surprising as the diameter of the lumen of tubules was estimated to be 0.1 μm previously (Levis and Deasy, 2002), enabling the dissolution medium to readily penetrate the lumen to promoted rapid outward diffusion of the drug. The final ~8% of drug was released at a much slower rate and probably corresponds to the ~2.4/28.5 =~ 8.4% ionic bound drug discussed above.

Fig. 3 shows comparative dissolution data for the less soluble cationic drug, propranol HCl, after

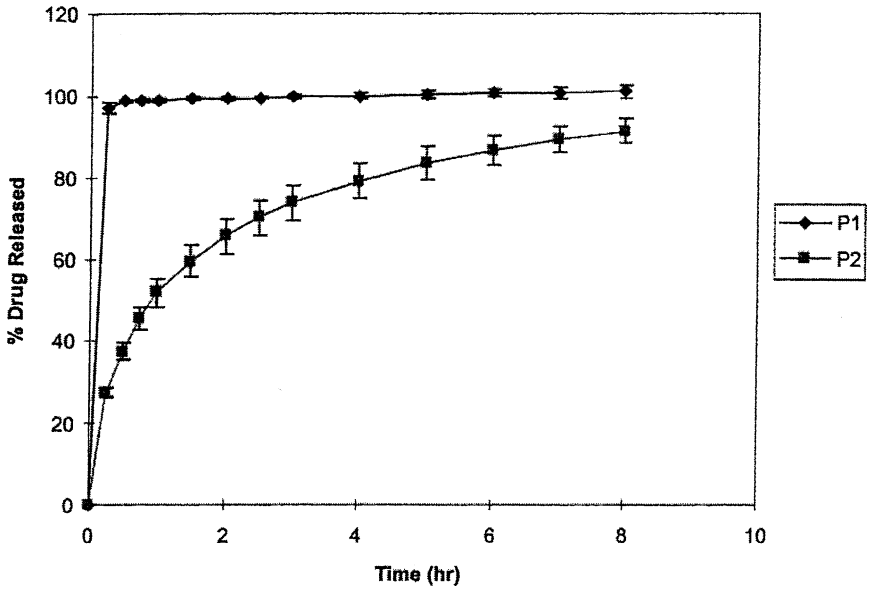

Fig. 3. Dissolution of diltiazem HCl (P1) and propranolol HCl (P2) from drug loaded halloysite at pH 6.8 for 8 h at 37 °C.

loading from a methanolic solution into halloysite, which causes significant retardation in release relative to the diltiazem HCl. The retardation in release caused by reduction in drug solubility is very apparent as only 80–90% of the propranol HCl loading in halloysite was released in 8 h, compared to ∼100% in 6 h for the diltiazem hydrochloride loaded halloysite. The effect should be even more marked with poorly soluble drugs.

In an attempt to further retard the diltazem HCl release from halloysite, the loading solution was thickened by adding 5 or 10% PVP, heating to effect solution of the polymer. Only a slight improvement in retarded drug release was observed, which was not deemed significant when similarity factors were calculated. A probable reason for the lack of effect of the added viscosity enhancer was that the loaded halloysite was dried to constant weight to recover it as a powder, causing both the drug and PVP to precipitate mainly within the lumen. Upon rehydration during dissolution testing, the PVP does not dissolve as rapidly as the drug and so the majority of the drug is leached out of the tubule before the increasing viscosity of the solution within it can fully exert its retardant effect.

3.3. Halloysite/chitosan binding studies

Initially the binding of cationic chitosan to anionic halloysite was studied to estimate the stoichiometry of the complex formed. Since the magnitude of the charge of both ionic species is highly pH dependent, the effect of two low pH values of the medium was examined, at which chitosan was soluble. Binding profiles were obtained by viscosity measurement as used by Takahashi et al. (1990) and the plots are shown in Fig. 4. It is apparent for both pH systems that as the ratio of chitosan to halloysite used increases, the specific viscosity also increases until a point of inflection occurs and a maximum specific viscosity level is achieved. This level is more evident when the experiment was performed at higher pH. The profiles are best explained by the fact that at high ratio, the amount of chitosan present is significantly greater than the amount of halloysite present. Almost all anionic sites on the halloysite surface are fully saturated or bound and the viscosity of the supernatant chitosan solution is very close to that of the original stock solution. As the ratio decreases, an inflection point is reached below which the amount of unbound anionic sites on the halloysite mineral increases dramatically, and so a greater proportion of the chitosan present is bound to the halloysite. This causes a pronounced decrease in the specific viscosity of the supernatant solution. Hence the point of inflection reflects the ratio of chitosan to halloysite that nearly saturates all available anionic binding sites on the mineral's surface. Ratios below this critical point represent only partial saturation, whereas those above represent near fully saturation.

The near complete saturation ratios, as indicated by points of inflection in Fig. 4, were similar at ∼0.1 for both pH systems. Hence binding ratios were constant despite the change in pH value, similar to the finding of Takahashi et al. (1990) for the binding between chitosan and sodium alginate. The degree of ionisation of halloysite decreases with decreasing pH (Levis and Deasy, 2002), whereas the ionisation

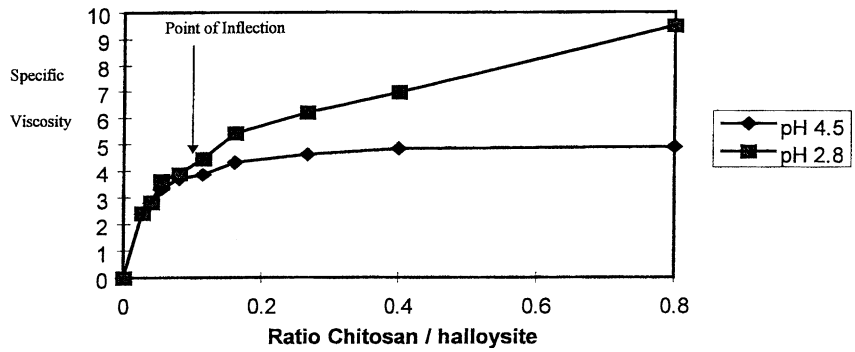

Fig. 4. Binding profiles, illustrating the effect of changing ratios of chitosan/halloysite on the specific viscosity of the supernatant chitosan solution, in buffer media pH 2.8 and 4.5.

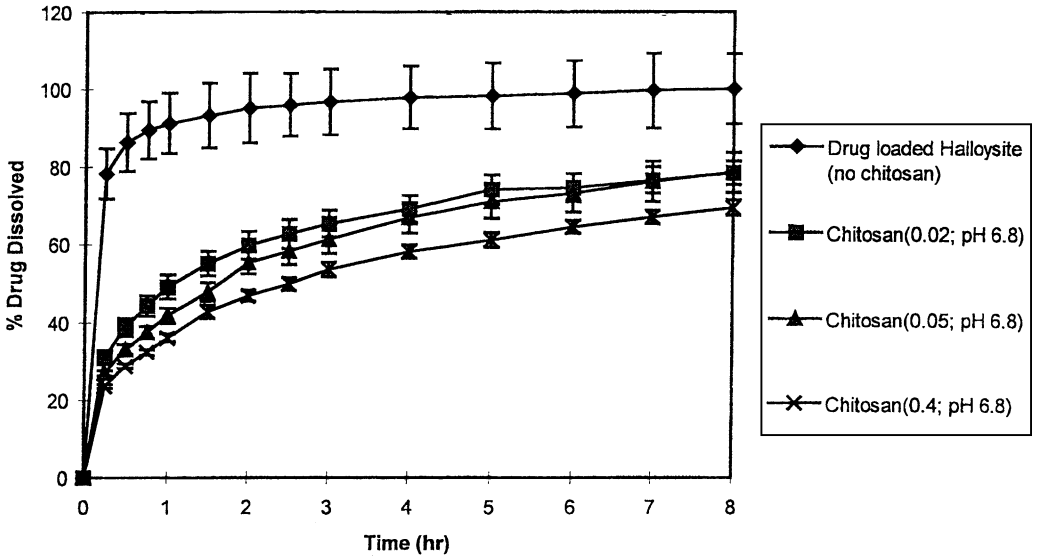

Fig. 5. Dissolution of diltiazem HCl from drug loaded halloysite, coated with chitosan (three levels, indicating the actual chitosan/halloysite ratio) or uncoated, at pH 6.8 for 8 h at 37 °C.

of chitosan increases. Hence it would be expected that the unit molecular binding ratio would alter with changing pH. As this was not observed at 37 °C, it may be due to the rigidity of the halloysite mineral, which Takahashi et al. (1990) observed to have an important role in polyion complex formation. However, the overall specific viscosity was higher in the aqueous solution of lower pH, due to greater protonation of available amino groups in chitosan, resulting in greater electrostatic repulsion between the solubilised chitosan molecules.

3.4. Cationic coated drug loaded halloysite

Three chitosan/halloysite ratios were examined at the higher pH of 4.5 for coating diltiazem HCl loaded mineral, two being below the point of inflection and representing incomplete neutralisation and film formation (0.02 and 0.05) and one above representing complete saturation and film formation (0.40). Dissolution studies were performed at two pH values, 3.2 and 6.8, and the results at pH 6.8 only are shown in Fig. 5. The results at pH 3.2 were qualitatively similar, though release rates for coated products were a little faster, as Singh and Ray (1999) have indicated that greater protonation of free amino groups at low pH causes chitosan molecules in films to uncoil, elongate and become more permeable. If data associated with the large burst effect occurring in the first 15 min was omitted, the remaining data gave significant correlation coefficients of greater than 0.97 ($P = 0.05$) for pseudo-zero-order drug delivery at all coating levels and pHs examined, suggestive of membrane-controlled release systems. Work by Singh and Ray (1999) demonstrated also that controlled release of glucose through chitosan membranes followed pseudo-zero-order release.

It is evident from Fig. 5 that as the ratio of chitosan to halloysite used to coat the loaded halloysite by competitive displacement of drug from surface binding sites, there was a progressive retardation effect on drug release, with the expected maximum effect apparent at the highest ratio used where maximum coating continuity should have been achieved. A pronounced burst effect was observed for all coated products (24–47% dissolved at 15 min for both pHs examined), probably due to the chitosan coating being applied in the form of an aqueous solution, which was capable of dissolving some of the entrapped drug causing it to become entrapped in the coating on subsequent drying before dissolution testing. This suggestion was confirmed by a large decrease in the drug encapsulation yield for

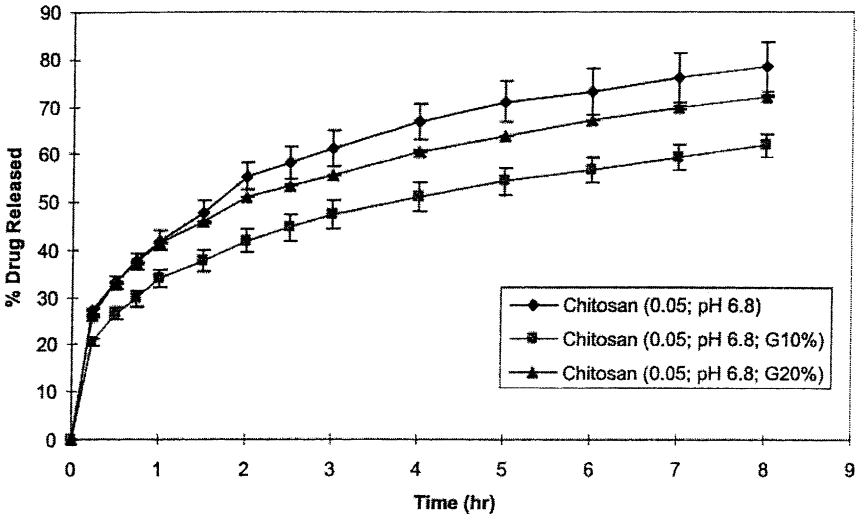

Fig. 6. Dissolution of diltiazem HCl from non cross-linked and cross-linked (10 and 20%, w/w glutaraldehyde) chitosan coated (0.05) drug loaded halloyisite at pH 6.8 for 8 h at 37 °C.

the uncoated halloysite (25.6%, w/w) to 7.8, 5.6 and 5.3% (w/w) for the 0.02, 0.05 and 0.40 ratios examined, respectively. As the chitosan/halloysite ratio increased, the encapsulation yield decreased, probably due to the thicker film formed around the halloysite particles, thus, increasing their overall weight and effective % drug loading. Increasing coating deposition tended to progressively reduce the burst effect. Similar burst effects have been observed with 5-fluorouracil loaded microspheres (Denkbas et al., 1999), where almost 50% of the drug loading was released within the first hour.

In an attempt to further delay drug release from the chitosan/halloysite 0.05 ratio coated drug loaded system, glutaraldehyde was incorporated as a cross-linking agent at 10 and 20% of the chitosan content into the coating solution immediately prior to application. The results for the dissolution profile obtained at pH 6.8 are shown in Fig. 6 indicating that the cross-linking treatment produced some additional

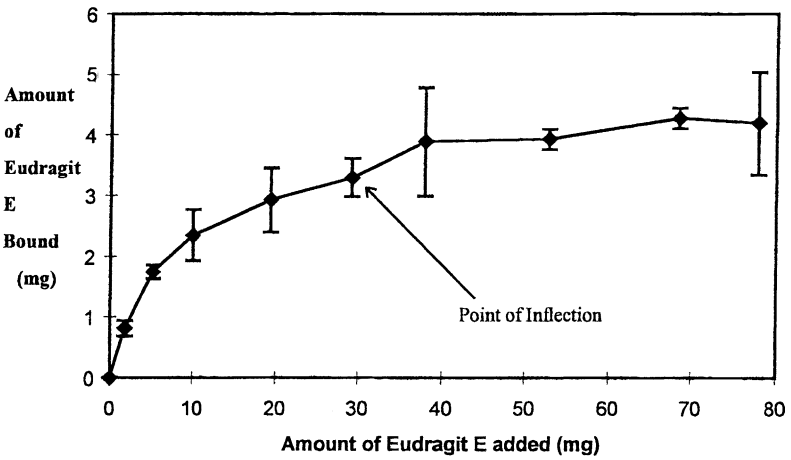

Fig. 7. Binding profile, illustrating the effect of changing amount of eudragit E (mg) added to halloysite (100 mg) on the amount of polymer bound.

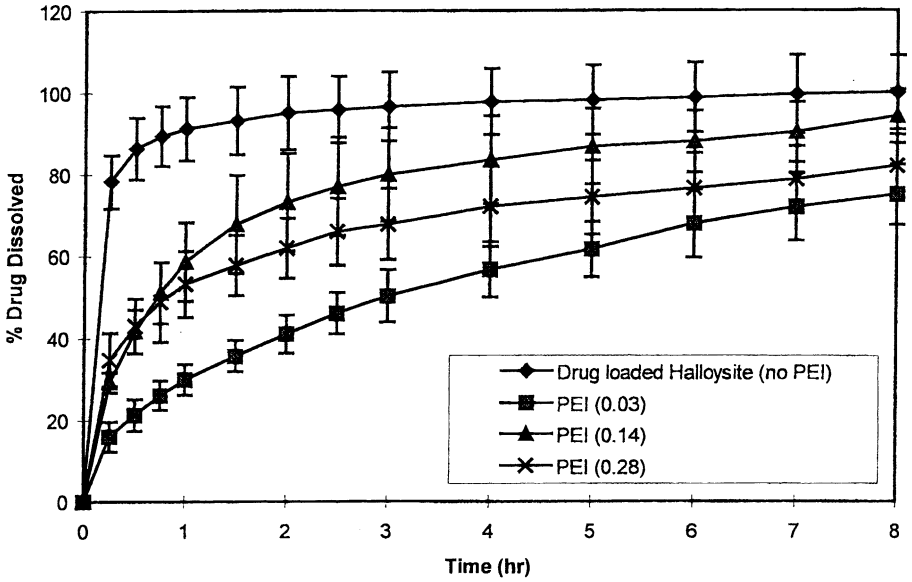

Fig. 8. Dissolution of diltiazem HCl from drug loaded halloysite, coated with PEI (three levels) or uncoated, at pH 6.8 for 8 h at 37 °C.

delayed release, as was also observed at pH 3.2. Excessive use of the cross-linking agent (20%) was less effective than the lower level examined, presumably by making the coating brittle and prone to crack prematurely, facilitating dose dumping. A similar effect was reported by Ganza-Gonzalez et al. (1999), who ascribed the effect partially to increasing formation of polyglutaraldehyde/chitosan copolymer with increasing glutaraldehyde addition, the resultant copolymer having more permeable hydrophilic domains. Thus, an optimum level of the cross-linker was required to maximise delayed drug delivery from chitosan coated halloysite, which level was not established in this study.

Two other cationic polymeric coatings were examined as alternatives to chitosan, namely eudragit E and PEI. Eudragit E is a polmethacrylate which is used frequently as a film former for taste and odour masking that becomes water soluble by forming salts with acids at low pH 2–5. A halloysite/eudragit E binding curve was constructed initially to study the polyion complexation, dissolving the polymer in 0.1 M acetic acid to effect solution and using UV analysis to determine the extent of binding as shown in Fig. 7. The profile was similar to that obtained with chitosan and based on this study three ratio levels were chosen for the coating of diltiazem HCl loaded halloysite, namely 0.025, 0.30 and 0.70, equating to below, approximately at, and above the inflection point. Dissolution studies were performed on the products at pH 3.2 and 6.8 and gave results generally similar to those obtained with chitosan.

A halloysite/PEI binding curve was constructed also to study the stoichiometry of the complexation by UV analysis, where the PEI was added as an aqueous solution to produce a profile similar to that obtained with chitosan. Three PEI/halloysite ratio levels were chosen for coating drug loaded halloysite, being 0.03, 0.14 and 0.28 corresponding to below, approximately at, and above the inflection point. The dissolution profiles at pH 6.8 of the products obtained are shown in Fig. 8. Whereas all the coated products had delayed release relative to the uncoated product, surprisingly the lowest coating ratio examined produced the maximum retardation of drug release with relatively little burst effect. A possible reason for this unexpected observation is that the architecture of the interaction between the clay mineral and the polycation was responsible as suggested by Lvov et al. (1996). When low concentrations of PEI are used (0.03), the individual molecules have more space for undisturbed movement. This allows the polycation to align with the

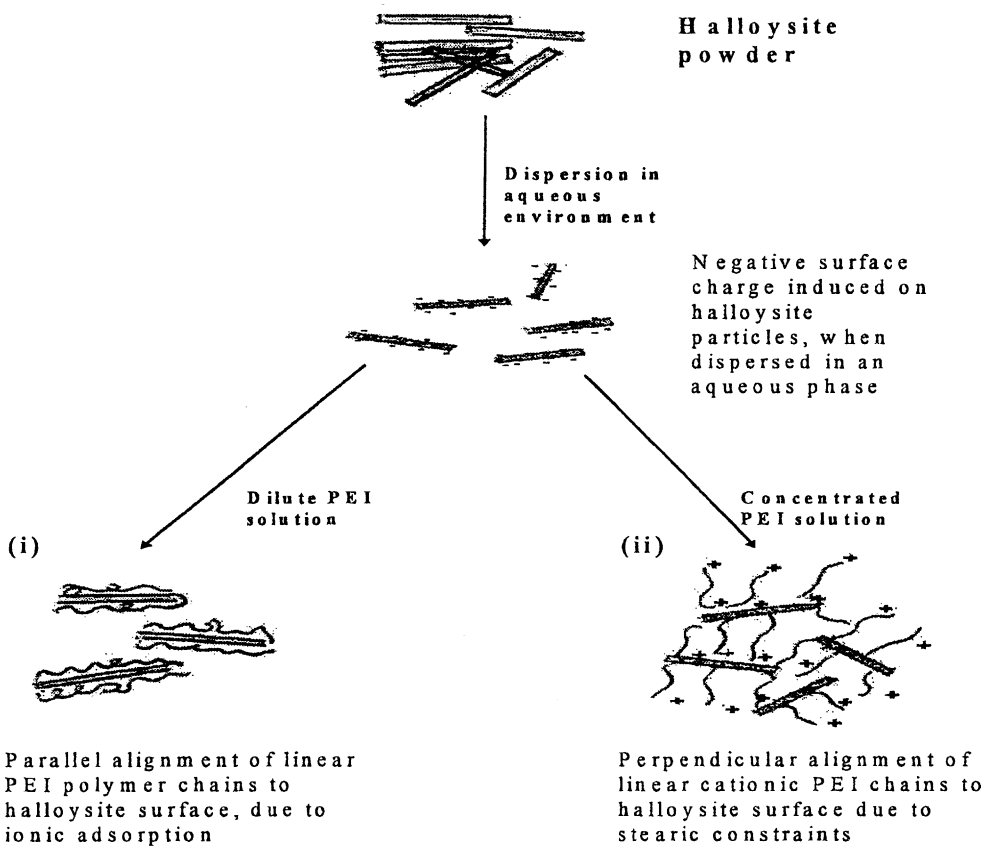

Fig. 9. Schematic representation of proposed binding patterns of the cationic linear PEI polymer to halloysite when (i) dilute and (ii) more concentrated aqueous solutions are used.

halloysite tubules as shown diagrammatically in Fig. 9 to create a thin but well organised dense film with good retardant properties. At higher levels (0.14 and 0.28), however, the polymer molecules are more constrained due to stearic difficulties created by reduced space. As a result, the polymer binds to the halloysite in a more random arrangement, and even though the film formed appears thicker, it is loose, less dense and more permeable. Whereas the optimum level of PEI to effect maximum retardation in drug release was not determined, PEI was not investigated further as it does not have regulatory approval for use in pharmaceuticals. However, in applications not subject to such constraints like agrichemical loaded halloysite, PEI should be a very useful coating material easily applied from dilute aqueous solution to produce prolonged release products.

3.5. Coating drug loaded halloysite using cyanoacrylate polymers

An alternative to the use of aqueous solutions of cationic coating polymers, should be the treatment of drug loaded halloysite with various alkyl-2-cyanoacrylate monomers dissolved in a water insoluble solvent like hexane, where gradual diffusion of monomer to the interface should lead to the progressive formation of a polymerised coating on the halloysite particles. The residual moisture content in the dried drug loaded particles before coating was estimated by TGA to be ~1.97%, which water should act as an initiator for the in situ polymerisation reaction. This coating technique should have the advantage over the aqueous charge neutralisation procedures examined, particularly for very water soluble

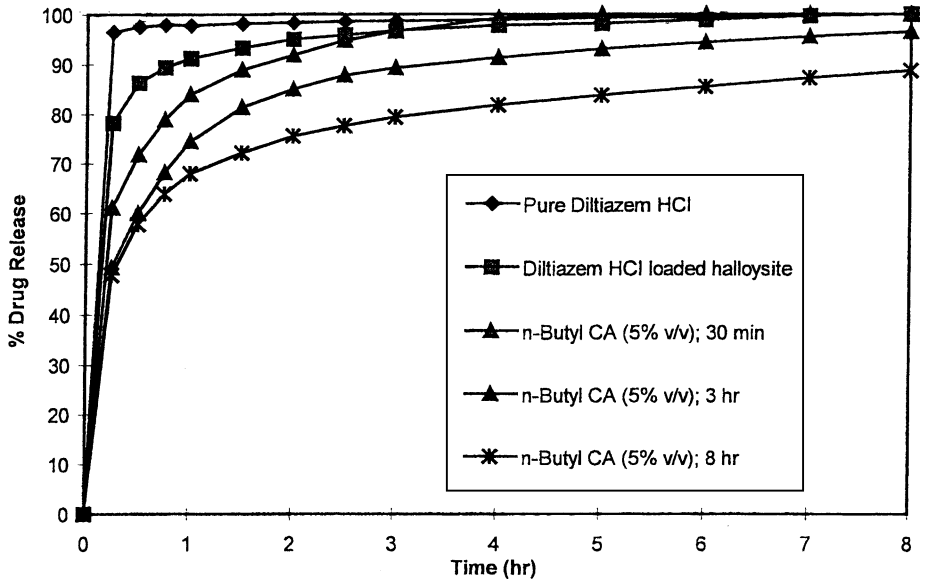

Fig. 10. Dissolution at pH 6.8 for 8 h at 37 °C of diltiazem HCl from drug loaded halloysite, coated with poly-*n*-butyl cyanoacrylate polymerised for 30 min, 3 or 8 h.

compounds like diltiazem HCl which is hexane insoluble, in not stripping the drug from the halloysite during the coating operation and, thus, preserving high loading. These biodegradable polymers are currently used as tissue adhesives and have been investigated extensively for drug delivery applications (Couvreur and Vauthier, 1991).

Fig. 10 shows the effect of polymerisation reaction time for 5% *n*-butyl cyanoacrylate applied on drug release from the coated diltiazem HCl loaded halloysite. The coated preparations all showed retarded drug release compared to free drug and drug loaded halloysite, longer polymerisation time tending to increase the effect presumably by forming thicker coatings as indicated by the % drug loading dropping from 18.51 to 18.0 to 17.83% for products coated for 0.5, 3 and 8 h, respectively. Longer polymerisation times also favoured the formation of polymers with higher average molecular weights, been determined as ~215,000, ~250,000 and ~550,000, respectively, larger molecular weight polymers been less biodegradable and less permeable during dissolution studies.

Fig. 11 shows the influence on drug release of using three different alkylcyanoacrylate monomers at 5% for coating, all with a polymerisation time of 8 h. The greatest retarded release was observed using the *iso*-butyl derivative, the other two monomers resulting in coatings with similar release profiles. If the burst effect associated with the initial 15 min was subtracted, the remaining dissolution data for the latter two products was best fitted to a pseudo-zero-order model, indicative of release from a coated reservoir device, whereas the poly-*iso*-butyl cyanoacrylate product was best fitted a square-root of time dependence, indicative of release from an inert matrix. This matrix was observed directly in transmission electron microscopy (TEM) studies for the poly-*iso*-butyl cyanoacrylate product only as shown in Fig. 12, where the drug loaded halloysite was shown to be dispersed in the polymer matrix, with individual tubules evident at the edge of the irregular particles recovered. GPC data confirmed also that the poly-*iso*-butyl coating had the highest average molecular weight (~720,000), compared ~550,000 and ~570,000 for the corresponding poly-*n*-butyl and poly-octyl coatings, thus, explaining its greater retardant effect.

The encapsulation yields for the poly-*n*-butyl, poly-*iso*-butyl and poly-octyl cyanoacrylate coatings, after polymerisation for 8 h from 5% monomer solutions, were 17.83, 18.75 and 21.46%, respectively, compared to 25.6% for the uncoated drug loaded

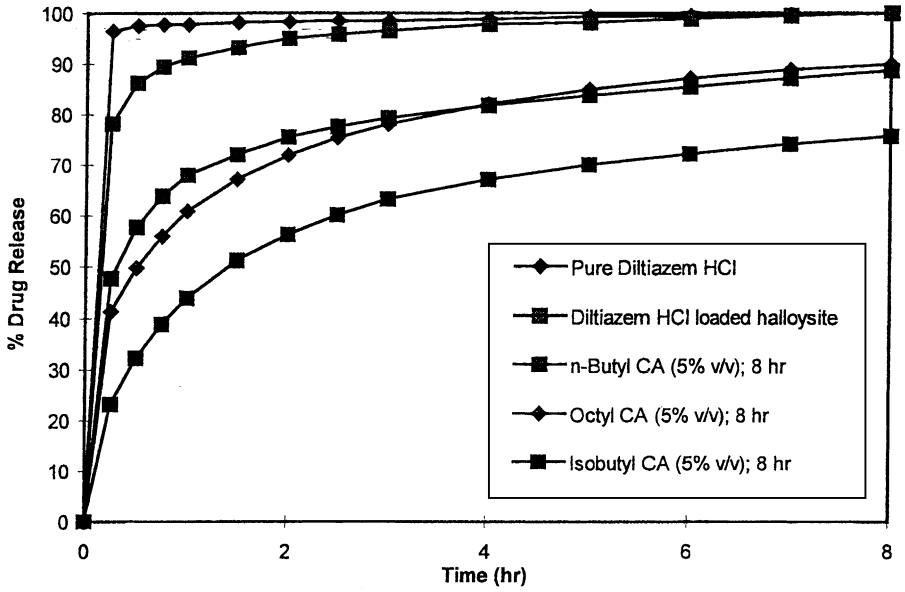

Fig. 11. Dissolution at pH 6.8 for 8 h at 37 °C of diltiazem HCl from drug loaded halloysite, coated with poly-*n*-butyl, poly-*iso*-butyl or poly-octyl cyanoacrylate polymerised for 8 h.

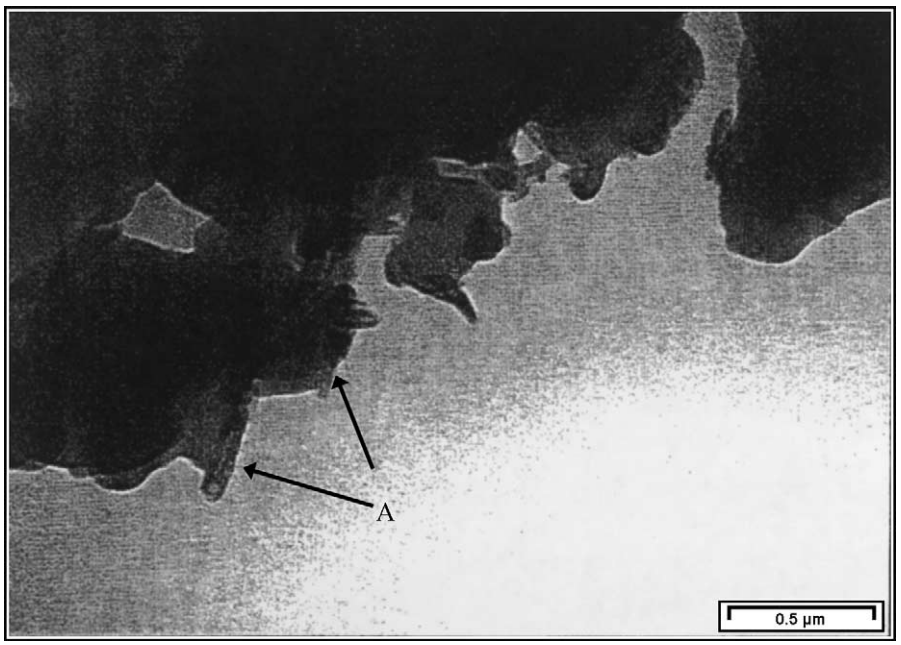

Fig. 12. TEM of poly-*iso*-butyl cyanoacrylate coated, drug loaded halloysite particles (70,000×). Individual halloysite microtubules are indicated (A).

halloysite. This indicated that the least polymer gain per unit mass of drug load halloysite occurred with the poly-octyl cyanoacrylate product as its encapsulation efficiency is closest to that of the uncoated halloysite powder. The specific polymer weight gains for the poly-*n*-butyl and poly-*iso*-butyl coated products are similar, suggesting that a major factor responsible for the delayed drug release of the latter is its higher average polymer molecular weight rather than overall coating gain.

4. Conclusions

The surface charge of the halloysite particles should have become reversed as a consequence of the polycation polymer coat binding, since polyelectrolyte concentrations used were sufficient to form a saturated layer. As a result, there should be potential to further delay drug release from these systems by subsequent application of alternating polyanionic and polycationic polymeric layers, thereby increasing the coating thickness and barrier property, as demonstrated in the research of Lvov et al. (1996) and Sukhorukov et al. (1998). Also other approaches to improving handling and modifying release from drug loaded coated halloysite could involve incorporation into solid lipid microparticles or pellet formation by extrusion/spheronisation. The results of these studies for a range of pharmaceutical and other applications will be published.

Acknowledgements

The halloysite used was supplied free by New Zealand China Clays, Auckland, New Zealand. Cyanoacrylate monomers where generously provided by Loctite (Ireland) Ltd, Dublin, who also determined the molecular weight of the extracted polycyanoacrylate coatings formed.

References

Couvreur, P., Vauthier, C., 1991. Polyalkylcyanoacrylate nanoparticles as a drug carrier: present state and perspectives. J. Control. Rel. 17, 187–198.

Denkbas, E.B., Seyyal, M., Piskins, E., 1999. 5-Fluorouracil loaded chitosan microspheres for chemoembolization. J. Microencapsul. 16, 741–749.

Ganza-Gonzalez, A., Anguiano-Igea, S., Gtero-Espinar, F.J., Blanco Mendez, J., 1999. Chitosan and chondroitin microspheres for oral-administration controlled release of metoclopramide. Eur. J. Pharm. Biopharm. 48, 149–155.

Levis, S.R., Deasy, P.B., 2002. Characterization of halloysite for use as a microtubular drug delivery system. Int. J. Pharm. 243, 125–134.

Lvov, Y., Ariga, K., Ichinose, I., Kunitake, T., 1996. Formation of ultrathin multilayer and hydrated gel from montmorillonite and linear polycations. Langmuir 12, 3038–3044.

Price, R.R., Gaber, B.P., Lvov, Y., 2001. In-vitro release characteristics of tetracycline HCl, khellin and nicotinamide adenine dinucleotide from halloysite; a cylindrical mineral. J. Microencap. 18, 713–722.

Singh, D.K., Ray, A.R., 1999. Controlled release of glucose through modified chitosan membranes. J. Membrane Sci. 155, 107–112.

Sukhorukov, G.B., Donath, E., Davis, S., Lichtenfeld, H., Caruso, F., Popov, V.I., Mohwald, H., 1998. Stepwise polyelectrolyte assembly on particle surfaces: a novel approach to colloid design. Polym. Adv. Technol. 9, 759–767.

Tang, Y., Gan, K., 1998. Statistical evaluation of in vitro dissolution of different brands of ciprofloxacin hydrochloride tablets and capsules. Drug Dev. Ind. Pharm. 24, 439–552.

Takahashi, T., Takayama, K., Machida, Y., Nagai, T., 1990. Characteristics of polyion complexes of chitosan with sodium alginate and sodium polyacrylate. Int. J. Pharm. 61, 35–41.

Yang, L., Fassihi, R., 1997. Examination of drug solubility, polymer types, hydrodynamics and loading dose on drug release behavior from a triple-layer asymmetric configuration delivery system. Int. J. Pharm. 155, 219–229.