

ORIGINAL ARTICLE

Optimization of diclofenac sodium profile from halloysite nanotubes

Optimalizace disolučního profilu diklofenaku sodné soli z halloysitových nanotubulů

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Summary

Halloysite, aluminosilicate clay with the particle shape of multilayered hollow nanotubes, used in various non-medical applications, e.g. in ceramic industry, was discovered for pharmaceutical purposes in recent years. Several drugs of hydrophilic and lipophilic nature have been successfully encapsulated into halloysite tubules in order to modify their dissolution profile. The main goal of this experiment was to optimize the dissolution profile of diclofenac sodium – a drug with problematic solubility – from halloysite tubules using various polymers. Loading of the drug together with povidone or Eudragit® RS did not lead to drug burst effect reduction and its slower dissolution. In the case of povidone, drug improved wettability and solubilization rather than viscosity increasing expectations were observed. Eudragit® RS formed a solid dispersion with diclofenac sodium and thus the solvent/drug solution penetration through the polymer and not the drug solubility was the dissolution rate limiting factor. Reduction of the burst effect and further prolongation of drug release was achieved by coating the drug-loaded halloysite with chitosan. This formulation exhibited a diffusion-controlled prolonged release following Higuchi kinetic model.

Keywords: halloysite • diclofenac sodium • povidone • Eudragit® RS • chitosan • solid dispersion • prolonged release

Souhrn

Halloysit, hlinitokřemičitý jíl s tvarem částic mnohovrstevných prázdných nanotubulů, používaný v různých nemedicínských aplikacích, např. v keramickém průmyslu, byl nedávno objeven také pro použití ve farmacii. Několik léčiv hydrofilní i lipofilní povahy bylo možné úspěšně enkapsulovat dovnitř halloysitových tubulů, a modifikovat tak jejich disoluční profil. Cílem našeho experimentu byla optimalizace disolučního profilu diklofenaku sodného – léčiva s problematickou rozpustností – z halloysitových tubulů s použitím různých polymerů. Enkapsulace léčiva s povidonem nebo Eudragitem® RS nevedla ke snížení burst efektu léčiva a jeho pomalejší disoluci. V případě povidonu se projevila spíše jeho schopnost zlepšit smáčivost a rozpouštění léčiva než jeho očekávané viskozitu zvyšující vlastnosti. Vzhledem k tomu, že Eudragit® RS tvořil s diklofenakem sodným pevnou disperzi, byla faktorem limitujícím disoluční rychlost penetrace rozpouštědla a roztoku léčiva spíše než jeho rozpustnost. Snížení burst efektu a další prodloužení uvolňování léčiva se dosáhlo obalením halloysitu s enkapsulovaným léčivem chitosanem. Složení tohoto vzorku vykazovalo prodloužené uvolňování diklofenaku sodného řízenou difuzí podle Higuchiho difuzního modelu.

Klíčová slova: halloysit • diklofenak sodný • povidon • Eudragit® RS • chitosan • pevná disperze • prodloužené uvolňování

Introduction

Halloysite is an interesting nanotubular material that can be utilized as a drug carrier due to its advantages such as biocompatibility, easy natural availability, high mechanical strength and especially drug binding properties. Drugs having a positive charge can be adsorbed onto the surface of hollow multilayered cylinders bearing a negative charge. Small polar drug molecules can be entrapped by intercalation in between the cylinders layers. The third and most important drug loading mechanism is tubular entrapment. Entrapped

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drugs can be protected against chemical or enzymatic degradation, their solubility can be either enhanced or their dissolution rate prolonged. Functionalized halloysite nanotubes containing drugs can be utilized in active ingredient targeting.

The encapsulation of several drugs, e.g. diltiazem hydrochloride and propranolol hydrochloride¹⁾, tetracycline hydrochloride, khellin and nicotinamide adenine dinucleotide²⁾, fentanyl base³⁾, 5-aminosalicylic acid⁴⁾, diclofenac sodium⁵⁾, into halloysite nanotubes was reported. In some cases, it was found necessary to add viscosity increasing excipient to aid the drug retention, like in the case of nicotinamide adenine dinucleotide and povidone. Dissolution of some highly soluble drugs (diltiazem hydrochloride) can be prolonged by coating of drug loaded nanotubes with polymers such as Eudragit® E, chitosan or polyethyleneimine. Due to negative charge of halloysite tubules, cationic polymers seem to bind readily to their surface area. Increasing coating thickness leads usually to slower dissolution rate of a drug. However, this is not the case in all coatings. Interesting finding was published by Levis and Deasy¹⁾ for polyethyleneimine. Here, surprisingly the very thin coating retarded the drug release the most. It was explained by the architecture of the interaction between the clay mineral and the polycation. When low concentration of the polymer is used, the individual molecules have more space for undisturbed movement. This allows the polycation to align with halloysite tubules to create a thin but well organized dense film with good retardant properties. At higher levels, however, the polymer molecules are more constrained due to steric difficulties created by the 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.

The aim of this work was to optimize diclofenac sodium (DS) dissolution profile from halloysite nanotubes as presented in previous experiment⁵⁾. In that study, we found that the drug release from loaded halloysite was retarded in comparison with the dissolution of the pure drug powder but with significant burst effect. In order to reduce this burst effect, cationic polymers, i.e. Eudragit® RS and chitosan, respectively, as well as viscosity increasing agent such as povidone were included in the formulations.

Experimental part

As starting materials for all experiments, diclofenac sodium (donated by Zentiva, a.s., Czech Republic), halloysite “G” clay mineral (NZ China Clays Ltd., New Zealand), Eudragit® RS 100 PO (Evonik, GmbH., Germany), povidone (Plasdone® K-26-28, BDH Laboratory Supplies, UK) and chitosan of medium molecular weight (Aldrich Chemical Co., Inc., Milwaukee, USA) were used. Methanol (VWR International Ltd., Poole, UK) and purified water were the solvents. For the preparation of dissolution media and buffers, citric acid monohydrate and disodium hydrogenphosphate dodecahydrate (Merck KGaA,

Darmstadt, Germany), acetic acid glacial and sodium acetate trihydrate (Sigma-Aldrich Chemie, GmbH, Germany) were used.

Determination of binding curves

The same procedure as described in our previous experimental work⁵⁾ was used. Briefly: 50 ml of aqueous drug solutions, containing various amounts of diclofenac sodium were added to 100 mg samples of sieved halloysite “G” powder or 200 mg Eudragit® RS 100 PO, respectively, and stirred for 20 min at 500 rpm. After sample filtration, UV analysis (Hewlett Packard 8452A Diode Array Spectrophotometer, Hewlett Packard Co., USA) was performed at 276 nm. The concentrations of DS in the solution were calculated for each sample using calibration curve. The difference in concentration of the drug solution before and after interaction corresponded to the amount bound to the halloysite or polymer material. All measurements were performed in triplicate.

Drug loading of halloysite

Adapted method of drug loading into halloysite as described in previous experiment⁵⁾ was involved. Briefly: sieved halloysite “G” clay mineral (< 185 µm) was loaded (in the ratio 3 : 5) with a 12% w/v drug solution in methanol which eventually contained 6% w/v of a polymer (either Eudragit® RS 100 PO or Plasdone® K-26-28). Vacuum was applied (vacuum pump Edwards Model RV5, Edwards High Vacuum International, UK) on the wetted halloysite powder in a sealed desiccator vessel until all gas bubbles were removed. The suspensions were subsequently filtrated to remove the residual drug solution and dried for 24 hours at the temperature of 60 °C. The dry samples were adjusted and sieved through a 185 µm sieve. The procedure was repeated once more to fill completely the inner space of mineral tubules with the drug.

Coating of the drug-loaded halloysite with chitosan

The appropriate amount of dried drug-loaded halloysite powder was placed into an Erlenmeyer flask and 0.2% w/v solution of chitosan in acetate buffer pH 3.7 was added. Levis and Deasy¹⁾ have found that the halloysite-chitosan interaction reaches near complete saturation when the ratio is 1:0.114. A higher coating ratio (0.4 g of chitosan per 1.0 g of halloysite) was chosen to ensure complete charge neutralization. After 2 min of mixing at 500 rpm, the suspension was filtrated and the residual powder was dried in a fan assisted oven at 60 °C for 24 hours, grounded down and sieved (185 µm).

Determination of the drug content

The amount of diclofenac sodium within samples (20 mg) was determined by extracting the drug into methanol in a 100 ml Erlenmeyer flask, keeping the samples at 37 °C for 72 h, occasionally shaken. Then the mixture was filtered through a 0.45 µm membrane filter (Supor®-450 membrane filter, Pall Corporation, USA) and the drug concentration was determined spectrophotometrically ($\lambda = 276$ nm) after reference to a pre-constructed calibration curve. Each determination was carried out in triplicate.

Preparation of Diclofenac Sodium – Eudragit® RS (DS-ERS) physical mixtures

The DS-ERS physical mixtures (1 : 9 w/w and 1 : 1 w/w, respectively) were prepared by simple mixing the two compounds in a mortar. The resulting powder was sieved and the < 250 µm fraction was collected.

Preparation of Diclofenac Sodium – Eudragit® RS solid dispersions (solvent method)

The DS-ERS co-evaporates, at different weight ratios (from 1 : 9 w/w to 9 : 1 w/w), were obtained by dissolving the drug along with the polymer (final weight 300 mg) in 3 ml of methanol. The solvent was then removed by its evaporation (30 min under vacuum followed by a fan assisted oven at 60 °C for 24 hours). The residue was pulverized and sieved. The absence of a residual solvent was checked by a TG analysis.

Differential Scanning Calorimetry (DSC)

The analytical method of DSC was employed to study the thermal properties, i.e. the endothermic and exothermic changes which occur when the sample is subjected to temperature changes. The DSC thermographs were obtained by using a DSC 821° apparatus (Mettler Toledo, GmbH., Switzerland) controlled by STAR° Software and calibrated using indium. Samples (5–9 mg) were precisely weighed in an aluminum pan and examined under nitrogen gas and scan rate of 10 °C per minute in the temperature range of 25 and 300 °C.

Thermogravimetric Analysis (TGA)

The mass change of the substance as a function of temperature was examined using thermogravimetric analysis. TGA was performed on powdered samples using a thermogravimetric analyser Mettler TG 50 coupled with a Mettler MT 5 thermobalance (Mettler Toledo, GmbH., Switzerland). The temperature range 25–300 °C with a heating rate 10 °C per minute was selected.

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra were recorded using a Nicolet Magna IR-560 Fourier Transform Infrared Spectrometer (Nicolet-Magna, USA) coupled with Omnic software for data analysis. The KBr disks were prepared by triturating KBr with dried finely powdered samples at 1% concentration (or 0.5% if necessary). The powder mix was spread uniformly in a suitable die and compressed under 800 MPa pressure (8 t.cm⁻²) for 2 minutes to form a transparent disk. The compressed samples were scanned from 600 to 4000 cm⁻¹.

X-ray Powder Diffraction Analysis (XRPD)

X-ray patterns were obtained using a Siemens D500 X-ray powder diffractometer (Siemens, Cambridge, UK). Powdered samples were studied by placing a thin layer of the powder in conventional cavity mounts. The samples were scanned from 5 to 40° 2θ. The CuK_{α1} anode (wavelength λ = 1.54056 Å) was operated at 40 kV and 20 mA. From X-ray scans, the d-spacings were calculated according to the Bragg's Law [Eq. 1]:

$$n\lambda = 2 d \sin\theta, \quad [\text{Eq. 1}]$$

where the integer n is the order of the diffracted beam, λ is the wavelength of the incident X-ray beam, d is the distance between adjacent planes of atoms (d-spacings), and θ is the angle of incidence of the X-ray beam.

Dissolution studies

The drug release from pellet or powder samples was measured using the basket dissolution apparatus Erweka DT-D6 (Erweka, GmbH, Germany). The dissolution profiles of 200 mg samples were determined in 1,000 ml of dissolution medium (purified water or McIlvaine's buffer pH 3.2 or McIlvaine's buffer pH 6.8, respectively) at a rotation speed of 100 rpm and the temperature of 37 °C. The powder samples were initially loaded into empty tea-bags and sealed at the opened end, before being placed into the basket. At predetermined time intervals, the samples (10 ml) were withdrawn, replaced with fresh medium, filtered and assayed spectrophotometrically (Lambda 25, Perkin Elmer, USA) at 276 nm. The dissolution test for each sample was carried out at least in triplicate. The data obtained were treated according to zero order [Eq. 2], first order [Eq. 3] and Higuchi's [Eq. 4] models:

$$M_t = M_0 + k_0 t \quad [\text{Eq. 2}]$$

$$\ln M_t = M_0 + k_1 t \quad [\text{Eq. 3}]$$

$$M_t = M_0 + k_H t^{1/2} \quad [\text{Eq. 4}]$$

In these equations, M_t is the cumulative amount of drug released at any specified time point, M₀ is the dose of the drug incorporated in the delivery system, k₀, k₁ and k_H are rate constants and t is time.

Results and discussion

Halloysite characterization

Raw halloysite G clay, as described⁵⁾, is a tinted yellowish to brownish powder with the determined apparent density of 2.291 ± 0.012 g . cm⁻³. To minimize the content of occasional agglomerates, sieving through a 185 µm sieve was employed and the < 185 µm sieve fraction only was used in the experiment. XRPD pattern of the halloysite G⁵⁾ sample showed that the halloysite sample was almost fully dehydrated to metahalloysite and this observation was supported also by the minimal weight loss (~ 3.79% ± 0.32%) during drying to the constant weight and TG analysis (~ 5.07% ± 0.70%) carried out on raw clay material.

Drug-loading mechanisms

Halloysite can interact with both organic and inorganic chemicals through a number of mechanisms such as adsorption, intercalation and cation exchange⁶⁾ or can enclose the drug by its mechanical entrapment within hollow cylinders. The permanent negative surface charge of clay minerals tends to electrostatically attract cations in order to ensure the electroneutrality of the system. However, alumina has a well-defined pH_{PZC} at about pH 7.6⁷⁾ and at the pH of the adsorption studies (the pH values of all halloysite bulk suspensions varied from 6.98 to

7.21), the presence of positively charged inner core surfaces and edges of the tubules cannot be excluded^{8,9}). In our experiment⁵), we found that the anionic drug could be adsorbed to some, albeit little, extent (~ 72 mmol/kg for diclofenac sodium). The second and much more important drug loading mechanism involved the tubular entrapment. The encapsulation efficiency of DS within the halloysite tubules was determined to be 48.1% (approx. 192.4 ± 6.7 mg of DS per gram of halloysite).

Coating of drug-loaded halloysite with chitosan

According to Levis and Deasy¹), drug-loaded mineral was coated with chitosan by a “charge neutralisation” process when chitosan adheres to the negatively charged mineral surfaces. Chitosan (CS), the N-deacetylated product of the natural polysaccharide chitin, is a well-known linear polycation where amino groups are readily available for chemical reactions and salt formation with acids. When two oppositely charged polyelectrolytes are mixed in an aqueous solution, a polyelectrolyte complex (PEC) is formed¹⁰). The 0.2% (w/v) solution of CS in acetic buffer pH 3.7 was used for the charge neutralization reaction. Under these conditions, DS is hardly soluble and its leaching from loaded halloysite tubules was reduced giving the encapsulation efficiency of 32.68% (~ 130.7 mg DS per 1 g of coated halloysite).

Dissolution studies

The solubility of DS is strongly influenced by pH, ionic strength and composition of the aqueous medium¹¹). As reported in the previous article⁵), DS dissolution was found to be highest in purified water due to the minimum ionic strength and absence of Na^+ ions coming from the buffer constituents, and it decreased with the decreasing value of pH as the drug is present more in its free acid form which is less soluble than the salt¹²).

DS-loaded halloysite: Similar dissolution behaviour of diclofenac sodium was observed also in the case of DS release from halloysite tubules. Fig. 1 shows the release profiles in three different dissolution media –

purified water, and McIlvaine's buffers pH 3.2 and 6.8 simulating gastric and small intestine pH conditions, respectively. The drug release from mineral tubules was retarded and the burst release reduced when compared with the dissolution of the pure drug powder. In buffered medium at pH 6.8, approximately 18% of drug still remained unreleased only even after 24 h of dissolution testing⁵).

DS-loaded with polymers: In an attempt to reduce burst DS release from halloysite, povidone (sample DS/PVP-LH) was added in a concentration of 6% w/v to the drug solution (12% w/v) used for drug-loading (EE $\sim 38.4\%$). As the movement of diclofenac sodium is controlled by diffusion, it was expected that the penetration rate of medium would be determined by the equilibrium between

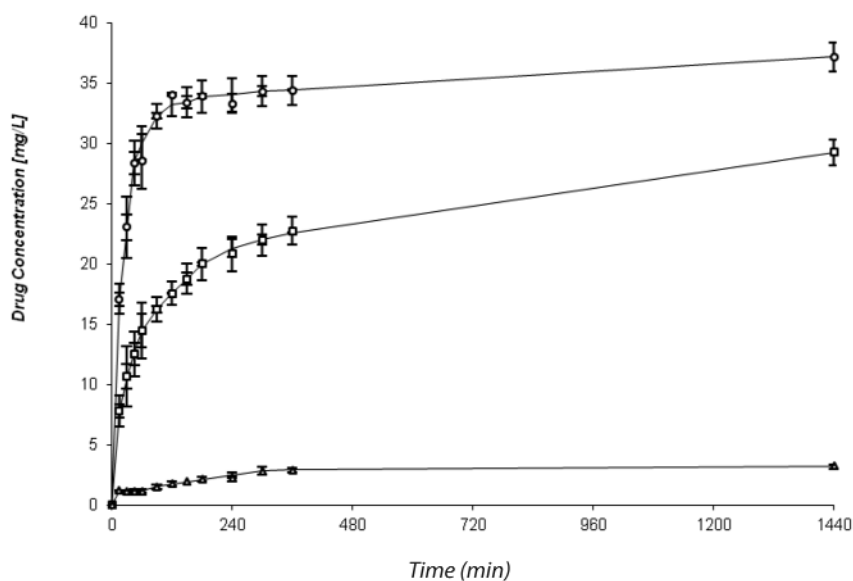


Fig. 1. Dissolution profile of diclofenac sodium from drug-loaded halloysite (sample DS-LH) in \circ purified water; \square McIlvaine's buffer pH 6.8; \triangle McIlvaine's buffer pH 3.2

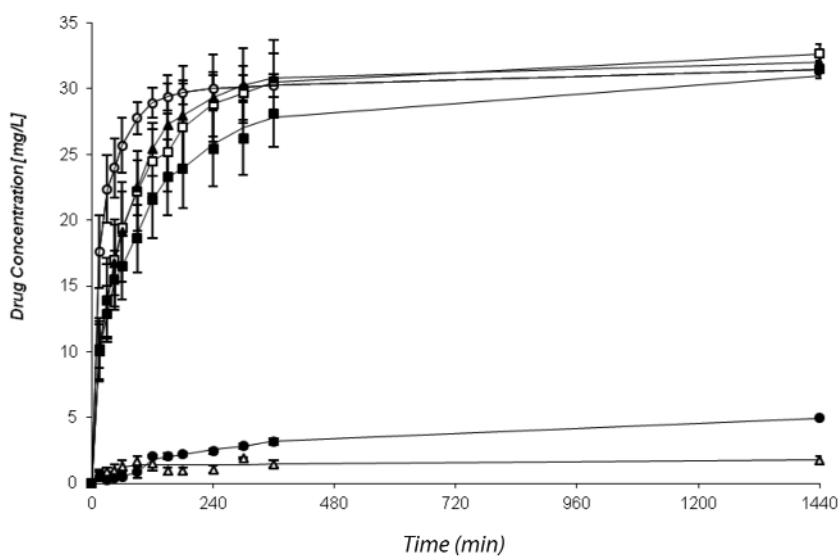


Fig. 2. Dissolution profile of diclofenac sodium release from sample DS/PVP-LH in \circ purified water; \square McIlvaine's buffer pH 6.8; \triangle McIlvaine's buffer pH 3.2; and sample DS/ERS-LH in \blacktriangle purified water; \blacksquare McIlvaine's buffer pH 6.8; \bullet McIlvaine's buffer pH 3.2
Note: drug concentration of 30.74 mg.l^{-1} (DS/PVP-LH) and 32.74 mg.l^{-1} (DS/ERS-LH) $\sim 100\%$ drug release

promotive forces of medium admission and those that act against its admission, i.e. viscosity forces which would be slower in a more viscous microenvironment exerted by hydration of PVP. When compared with the dissolution profile of drug loaded halloysite (sample DS-LH, Fig. 1), negligible retard effect was observed for the polymer addition under pH 3.2 (Fig. 2). Dissolution of diclofenac sodium from sample DS/PVP-LH was faster in purified water and in buffer of pH 6.8. This observation can be explained by other well-known properties of povidone such as drug improved wettability and solubilization effects¹³, rather than viscosity increasing expectations connected with slower drug release. Due to its chemical structure, povidone forms chemical complexes with a number of substances, including the drugs. These complexes almost always dissolve more readily or more quickly than the pure drug. Povidone is known to improve solubility of drugs also in their physical mixtures or solid dispersions¹⁴.

The concept of solid dispersion was explored using a water-insoluble carrier material - Eudragit® RS 100 PO (ERS). As previously reported¹⁵, these systems loaded with hydrophilic drugs lead to delivery systems aimed at optimising pharmacokinetics and reducing drug side-effects (e.g. the gastric irritation of some non-steroidal anti-inflammatory drugs). ERS is a copolymer synthesized from acrylic and methacrylic acid esters, containing a low level of quaternary ammonium groups (~ 4.5–6.8 %). As a consequence, it is insoluble at physiological pH values, is able to swell and become permeable to water¹⁶. In these systems, the drug is either dissolved or uniformly dispersed within the ERS matrix. When Eudragit® RS was

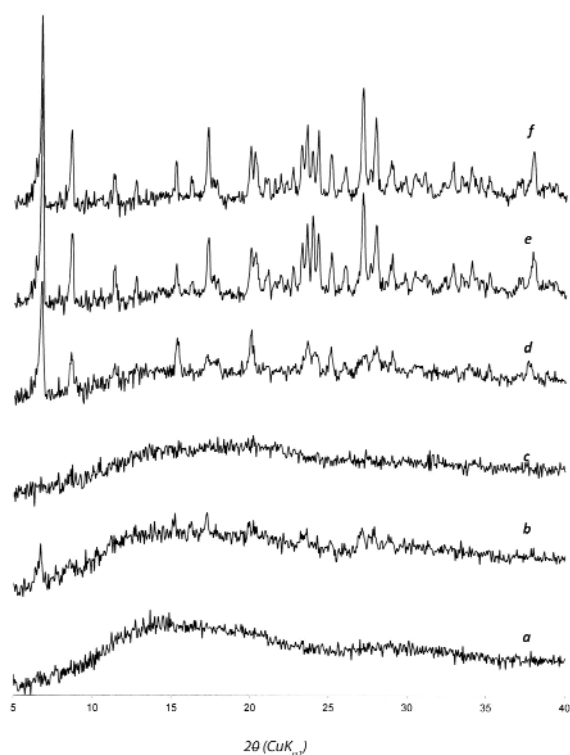


Fig. 3. XRPD spectra of (a) Eudragit® RS PO, (b) 1:9 (w/w) DS/ERS physical mixture, (c) 1:9 (w/w) DS/ERS co-evaporate, (d) DS/ERS 1:1 (w/w) co-evaporate, (e) diclofenac sodium-co-evaporate from methanol and (f) diclofenac sodium raw

used in our samples, the dissolution profiles in both purified water and buffer pH 6.8 were similar suggesting that more solvent/drug solution penetration through the polymer than the drug solubility could be the rate limiting factor. At the beginning of the dissolution process, the active substance at and near the surface dissolved quickly giving approx. 30% burst release (Fig. 2). When the dissolution continued, the diffusion process slowed down and reached a plateau as a consequence of increased diffusional path length and bigger resistance towards the solvent penetration caused by the polymer. To help understand the mechanism of drug release from this formulation, the data were treated according to different kinetic models. The data gave the best fit (correlation coefficient $R = 0.959$) for Higuchi model suggesting that the drug release exhibited a matrix diffusion-controlled mechanism. Many papers^{17, 18} have described the possible interactions between the drug molecule and the Eudragit® RS polymer structure. In particular, the incorporation and release of non-steroidal anti-inflammatory drugs from ERS polymer was shown to be strongly dependent on the acidic nature of these drugs. The presence of the carboxyl group allows chemical and/or physical interactions (zwitterionic adducts, ion pairs, ion exchange resin behaviour) to occur with the ammonium group of ERS polymer in the solid dispersion¹⁸. Being a simple surface physical adsorption or a true chemical reaction, such interactions can affect the state of drug dispersion in the system and its subsequent release rate¹⁵. Therefore, the possible interactions occurring between diclofenac sodium and ERS polymer were investigated. Results obtained from DSC and XRPD analysis suggested some interactions in terms of solubilisation, between the polymer and the model drug, i.e. all the drug in a solid dispersion might not necessarily be present in a microcrystalline state; a certain fraction of the drug might be molecularly dispersed in the matrix, thus forming a solid solution¹⁹. The approximate solubility of

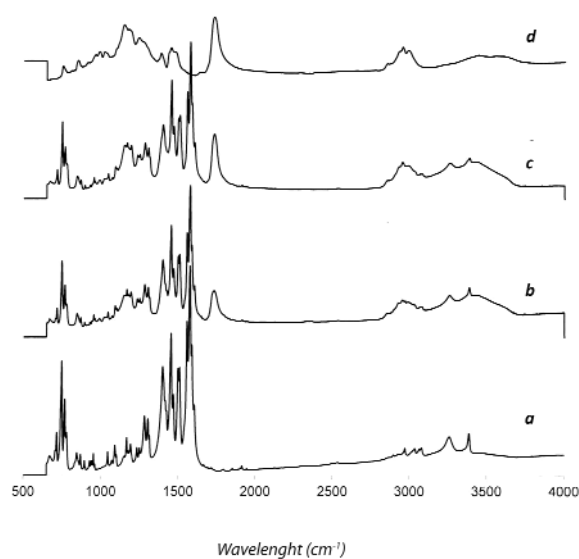


Fig. 4. FTIR spectra of (a) pure drug, (b) diclofenac sodium-Eudragit® RS (1:1 w/w) physical mixture and (c) appropriate co-evaporate from methanol and (d) Eudragit® RS

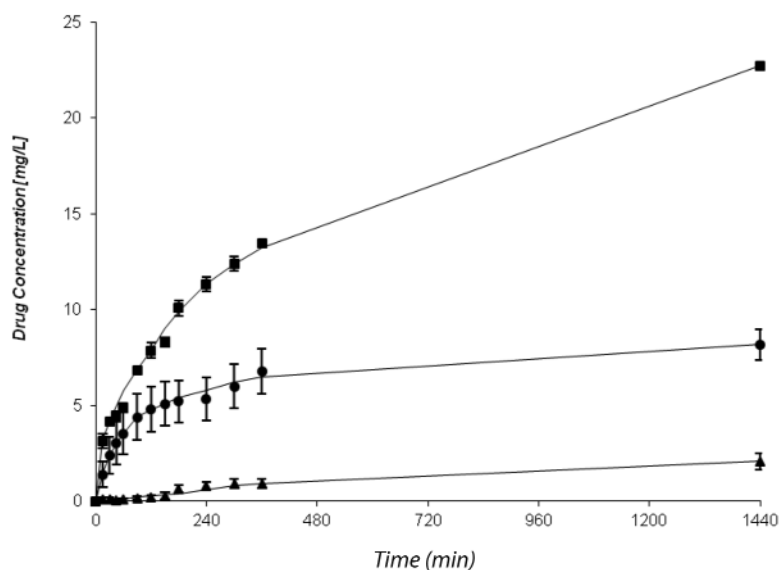


Fig. 5. Dissolution profile of diclofenac sodium release from sample DS-LH-CHC in ● purified water; ■ McIlvaine's buffer pH 6.8; and ▲ McIlvaine's buffer pH 3.2
Note: drug concentration of 26.14 mg.l^{-1} ~ 100% drug release

DS in ERS polymer was determined according to Jenquin and McGinity²⁰ when the percentage of the drug in solid dispersion was plotted against the normalized endothermic energy of melting. The approximate solubility of diclofenac sodium in ERS was found to be 15.4% (w/w). The X-ray diffraction pattern of 10% drug-polymer co-evaporate (Fig. 3) was devoid of any peak associated with any crystalline drug and was rather similar to that one of pure polymer. As the XRPD pattern of drug crystals subjected to the same evaporation process used in the solid dispersion preparation exhibited sharp diffraction peaks caused by the presence of crystalline drug, it could be concluded the evaporation process itself did not induce changes in the crystalline state of the drug. The reappearance of sharp diffraction peaks in the pattern of 50% DS/ERS co-evaporate when the drug concentration exceeded its polymer solubility suggested that at 10% drug loading, the drug is probably dissolved in the acrylic carrier and the matrix existed as a solid solution.

Fourier transform infrared spectroscopy was employed to study the drug-polymer dispersion for changes in the molecular structure. Infrared spectra of 50% physical mixture and appropriate co-evaporate (Fig. 4b and 4c, respectively) were not dissimilar to the simple superimposition of diclofenac sodium (Fig. 4d) and ERS infrared patterns (Fig. 4a). This suggests that the formation of covalent chemical bonds did not occur.

The theoretical mechanism of interaction being predominantly an ionic electrostatic binding between the anionic drug molecule and cationic quaternary ammonium groups of the polymer was supported by the results of adsorption studies. From the adsorption curve plateau, the maximal amount of DS being adsorbed onto

Eudragit® RS was found to be $\sim (27.2 \pm 0.3)$ mg per gram of the polymer.

Chitosan coating: The slower and incomplete drug release from chitosan-coated halloysite in purified water (see Fig. 5) could be explained in terms of DS-CS complex formation. Polycationic CS molecule, though bound to the halloysite surface, could still have the capacity to bind anionic molecules by an ionic reaction. Being the salt of a weak acid, diclofenac sodium has the functional group of $-\text{CH}_2\text{COO}^-$ in its binding sites, interacting with chitosan through its $-\text{NH}_3^+$ groups. The interaction of CS with DS could lead to the formation of a complex. In the environment of McIlvaine's citrate-phosphate buffer (pH

6.8), DS could compete for binding sites and be replaced by the ionized form of a stronger citric acid (citric acid dissociates into three degrees: $\text{pKa (I)} = 3.12$; $\text{pKa (II)} = 4.76$; $\text{pKa (III)} = 6.39$ ²¹). This could explain faster and almost complete drug release from CS-coated halloysite in this buffered medium. The formulation exhibited a diffusion-controlled sustained-release fitting square-root-time kinetic ($R = 0.991$). Therefore, the drug release rate would be controlled by the extent and rate of water penetration into mineral tubules, swelling of the chitosan layer and the rate of diffusion of the active compound through the CS hydrogel formed.

Conclusions

The optimization of the dissolution profile of diclofenac sodium from halloysite nanotubules using several polymers was the goal of this experiment. Loading of the drug together with different polymers (PVP or ERS) did not lead to more extensive drug-release retardation as originally expected. This observation could be explained in terms of solid dispersion formation. Significant reduction of the burst release and further delay of the drug release was achieved by coating the drug-loaded halloysite with chitosan. This formulation exhibited a diffusion-controlled sustained-release following a square-root-time kinetic model.

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Conflicts of interest: none.

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