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Release kinetics of 5-aminosalicylic acid from halloysite

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ABSTRACT

This paper investigates desorption of 5-aminosalicilyc acid (5-ASA) adsorbed onto halloysite (HL). Desorption isotherms were fitted according to kinetic laws obtained considering release of 5-ASA from HL as the phase of desorption of the previously adsorbed drug molecules both inside the nanotubes of HL as onto the surface of clay particles and/or in the inter-particle spaces of their aggregates [28]. Desorption isotherms has been also fitted with other equations frequently used in drug release kinetics studies. The best fitting corresponded to the kinetic model proposed; in agreement with the results of adsorption [28].

1. Introduction

Modified drug delivery systems are ideally designed to improve therapeutic efficacy in comparison with conventional dosage forms. They are aimed to maintain therapeutic drug concentrations at the site of action, to minimise side effects and/or regulate release kinetics. Many drug carriers have been described for these purposes, being polymeric systems the most studied [1–6]. However, porous inorganic materials, including silicon derivates, can show several advantages in drug delivery applications [7–9]. Combination between organic polymers and silicates are also attractive candidates for drug delivery, because they can display advantageous chemical and physical characteristics not exhibited by the individual constituents [10,11].

A number of reviews show that mathematical analysis of *in vitro* dissolution data can provide a scientific basis in the understanding of mechanisms of mass transport involved in drug release from modified drug delivery systems [12–20]. Nevertheless, it should be stressed that there is no universal mathematical model that can explain all the possible physical and chemical processes of drug release. A given model can indeed describe a given delivery system under well-defined conditions, beyond which it cannot be considered predictive. The predictive capacity and accuracy are key features for a model. Empirical models can be very flexible but they are not sufficient to predict the exact behaviour of drug release. When possible, mechanistic theories should be applied because they can explain release mechanisms. Many efforts were directed to the study of models aimed to describe the kinetics of drug release from polymeric matrices, especially in the case of heterogeneous systems. In 1961, Takeru Higuchi published what is likely to be regarded as the most famous mechanistic equation used to fit drug release [21]. The "Higuchi model", initially valid only for systems with laminar geometry, was subsequently extended to other geometries and modified to consider different features, such as porosity [22–26]. Despite these improvements, it can be taken into account that most of the hypotheses postulated by this model are not reflected in real systems. The main advantage of the Higuchi equation, however, lies in its simplicity and it is often used for the analysis of dissolution data from a variety of dosage forms, providing approximate information about mechanisms that govern drug release. Widely used in the study of dissolution kinetics from controlled release polymeric matrices is also the so-called "power law" [27]. However, due to the complexity of the phenomena to be described, much more efforts are needed to devote to searching for real (mechanistic) models apt to adequately interpret the kinetics of dissolution from drug delivery systems. In particular, no models have been yet developed to describe drug release from porous inorganic solid sorbents.

With these premises, in this work a new mechanistic model was proposed, based on adsorption–desorption equilibrium between a model drug (5-amino salicylic acid) and an inorganic support (halloysite).

Halloysite is a naturally occurring aluminosilicate, chemically similar to kaolinite, having predominant hollow tubular morphology. Thanks to its special morphology, halloysite has been used as carrier for drug encapsulation [28–31]. The *in vitro* release characteristics of different drugs from halloysite tubes have been described in the literature, showing sustained release properties in

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almost all cases [32,33]. It has been also demonstrated that coating the halloysite using cationic polymers can further enhance the retardation of drug release [34,35].

5-Amino salicylic acid (5-ASA) (also known as mesalazine) is an anti-inflammatory agent widely used in the therapy of ulcerative colitis and Crohn's disease. It can be administered orally, but it needs to be protected in order to limit the absorption in the upper gastrointestinal tract (stomach and small intestine) [36]. For this purpose, equilibrium, kinetics and thermodynamic aspects of adsorption of 5-ASA into halloysite tubes was investigated [28]. The drug was adsorbed by the inorganic support as a result of two subsequent processes: rapid adsorption (specific adsorption rates between 10.0 and 12.3 s^{-1}; $\Delta H = 7.59$ kJ/g) on the external clay mineral surface followed by slow adsorption (specific adsorption rates between 0.2 and 0.4 s^{-1}; $\Delta H = 42.28$ kJ/g) inside the halloysite tubes. The structure of the obtained loaded tubes was detailed by solid state characterisation techniques, including high resolution electron microscopy (HREM) coupled with analysis X-ray energy dispersive spectroscopy (X-EDS) and confirming the presence of the drug both at the surface and inside the halloysite tubes [31].

With these premises, in this work, *in vitro* release behaviour (mechanisms and kinetics) from 5-ASA halloysite adsorbate was examined on the basis of desorption kinetics. The satisfactoriness of the fitting was expressed by the correlation coefficient (R^2). The results have been compared with other equations, widely used in literature for release kinetic studies (first order, Higuchi or "square root", Hixson and Crowell or "cube root", Peppas or "power law" and Weibull) widely described in the literature [21,27,37–40]. Comparison was done using adjusted correlation coefficients (R^2_{adj}), where R^2 values were normalised as a function of the number of experimental points and parameters of each equation [14].

2. Experimentals

2.1. Materials

5-ASA analytical grade (Sigma Aldrich, Spain) was used as supplied.

Halloysite (HL) from Zaragoza deposits (Spain) was kindly gifted by the Department of Inorganic Chemistry (Faculty of Sciences) of the University of Granada. It was milled (Ika®-Werke mill M20, GMBH & Co. KG, Germany) and sieved (125–250 μm) to eliminate coarse particles and aggregates. Porosity of HL showed a bimodal profile in the range 10–0.06 μm, the outer diameters of the individual tubes being about 0.1 μm and the specific surface area approximately 45 m^2/g [31].

2.2. Sorption of 5-ASA onto HL

5 g of HL were dispersed under stirring (100 rpm) in 500 ml of 5-ASA aqueous solution (225 mg/l) at 40 ± 0.1 °C for 24 h. This time was long enough to ensure that equilibrium was reached between the drug adsorbed and drug in solution [28]. The adsorbate (hereafter referred as 5-ASA-HL) were recovered by filtration and dried in oven at 60 °C. The amount of drug retained was determined by UV spectroscopy at 297 nm (Perkin Elmer®, Lambda 25, Barcelona, Spain), resulting in approximately 4 mg/g dried HL.

2.3. Desorption studies

Desorption isotherms (weight/weight % of drug released *vs* time) were obtained on the base of "Dissolution Test procedures" for "Oral Solid Dosage Forms" [41]. Measurements were done on 2 g of adsorbate powder (<125 μm sieve fraction) using a AT7 automatic dissolution tester (Sotax, Spain) into 700 ml of dissolution medium (maintained at 37 °C), rotating at 50 rpm by means of the USP apparatus II. Three different media (purified water, 0.1 M HCl and pH 6.8 buffer (0.1 M HCl:0.2 M Na_3PO_4 3:1 v/v)) were considered in order to evaluate the influence of pH and ionic strength on the release behaviour of the drug. Desorption was also studied following the USP method A for drug release of enteric-coated dosage forms. In this case, 525 ml of 0.1 M HCl were initially placed in the vessels (acid stage); after 2 h, 125 ml of 0.2 M tribasic sodium phosphate were added to the acidic solution giving a final pH of 6.8 (buffer stage) and a total volume of 700 ml.

At fixed times, 2 ml of dissolution media were automatically withdrawn (piston pump CY 7-50, Sotax, Spain) and collected in test tubes prior to be analysed (fraction collector C613, Sotax, Spain) by HPLC. Total amounts of drug released (Q_t) were calculated as follows:

$$Q_t = V_m C_t + \sum_{i=0}^{t-1} V_a C_i \quad (1)$$

where V_m and C_t are volume and concentration of the drug at time t, V_a is the volume of the sample withdrawn and C_i is drug concentration at time i ($i < t$).

2.3.1. Drug assay

The amount of drug dissolved was assayed by HPLC (series 200B/250, Perkin Elmer, Spain) according to [42]. The stationary phase was a Kromasil® C18 column (5 μm, 250 mm × 4.6 mm) (Teknokroma, Spain) and the mobile phase was a mixture of H_2O/CH_3CN (78/22, v/v) and acetic acid 0.5% (v/v). The flow rate was set at 1 ml/min, the injection volume was 20 μl, the detector wavelength 297 nm and the run time 5 min. Data were recorded and processed using TotalChromWS6.2 software package (Perkin Elmer, Spain). The analytical method was validated by determining analytical (linearity, detection limit, quantification limit, repeatability) and suitability (column efficiency, tailing factor) parameters according to the indications of ICH and USP.

3. Results and discussion

3.1. Analytical results

Retention time of 5-ASA in all the dissolution media considered in this study was approximately 2.5 min. The detector response was linear in the range 5–100 μg/ml in all the media (five data points, replicated three times, have been considered). Analytical and suitability parameters, calculated according to ICH and USP recommendations, are given in Table 1. The slope of the curve obtained by plotting the log of drug concentration *vs* the log of peak area (log–log slope) fulfilled ICH recommendations (0.95–1.05 accepted interval) in all the media, with a variation coefficient ≤1%. The limits of detection (LD) and quantification (LQ), determined from the signal-to-noise ratio, were <1 μg/ml. Repeatability (variation within-day) of peak area (A) and retention time (t_R), expressed as relative standard deviation (S_R), was always ≤1%. It was determined on the basis of nine analyses (three concentrations/three replicates each) of 5-ASA standard solutions covering the linearity range in all the media. Column efficiency, expressed as the number of theoretical plates (N), was about 8000 and tailing factor (T) was in the range 0.9–1.1, indicating that suitable peak symmetry was reached in all the media. Extraction recoveries were satisfactory and greater than 97% (ranging from 97.8% to 99.2%) for all samples tested.

3.2. Desorption isotherms

Desorption isotherms of 5-ASA-HL in water, pH 1.0 (0.1 M HCl) and pH 6.8 showed biphasic behaviour with turning points at