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Theoretical and experimental studies on theophylline release from hydrophilic alginate nanoparticles

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Abstract

Background: Mathematical modelling may be able to reduce the number of in vitro experiments and provide an insight into the elementary physical and chemical mechanisms that regulate the rate and degree of drug release. The aim of the present examination was to develop a simple mathematical model to portray drug release from the alginate-type hydrophilic matrix, taking into account the Fickian diffusion of drug and swelling of the matrix using theophylline as the model drug.

Results: The nanoparticles show a remarkable swelling in the simulated intestinal fluid. The theoretical drug release values were validated with experimental values by considering diffusion and diffusion with swelling. The experimental value fitted well with the theoretical value predicted based on diffusion. It was found that after 3 h, the entire drug release followed a pure diffusion transport.

Conclusions: The numerical model was found to be sufficiently accurate in guessing the drug release from the alginate matrix. The developed model could be extended to quantitatively prognosticate the drug release from hydrophilic spherical matrices.

Keywords: Matrix, Diffusion, Swelling, Modelling

Background

During the last decades, drug delivery systems have received considerable attention [1–4]. These systems are intended to offer controlled administration of the pharmaceutical compound to keep their concentration within the therapeutic range. Additionally, they help to reduce the number of drug dosages, initial drug concentration, and side effects due to the unspecific systemic distribution of drugs [5–7]. In vitro drug release studies have been considered as a vital component in the pharmaceutical formulation development. Preliminary data obtained from these studies facilitate the design of the system with optimal in vivo performance. In vitro experiments with varying parameters are required to optimize the device design.

Mathematical modelling may be able to reduce the number of in vitro experiments and provide a perception of the underlying physical and chemical mechanisms that govern the rate and degree of drug release [8]. Diffusion characteristics, distribution pattern, and loading of a drug in the matrix affect the kinetics and mechanism of drug release [9]. Drug diffusion is significantly influenced by the topology and swelling nature of the matrix. Upon contact with body fluids, the polymer swells and the active ingredient diffuses through the network meshes [10]. The diffusional mass transport assumes a critical part for overcoming the key hindrances, such as mucosa in the gastrointestinal tract [11].

The mathematical model suggested by Higuchi in 1961 based on diffusion mechanism was the first to describe drug release from a matrix system [12]. It may be able to explain the drug release from various pharmaceutical dosage forms [13]. Numerous other models were also formulated to describe the release mechanisms from various polymeric drug delivery systems and most of them involve

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sophisticated mathematical expressions to depict the drug release pattern [14–20]. However, only limited studies have been reported to examine drug release mechanisms from hydrophilic polymer matrices [21, 22].

Alginate (ALG) is a hydrophilic carrier used for the development of oral controlled drug delivery systems. ALG displays a pH-dependent swelling in biological fluids. This property makes alginate an attractive candidate for oral drug delivery applications where the system has to pass through the acidic and alkaline environment [23]. In order to find its application in the pharmaceutical discipline, a detailed knowledge of drug release mechanism and swelling is needed [24]. Even though the swelling nature of alginate was examined by several groups [25–29], only a limited number of mathematical modelling were made on these types of polymer matrix systems [9].

The goal of the current study is to develop a simple mathematical model to describe the drug release from the alginate-type hydrophilic matrix, considering the Fickian diffusion of drugs and swelling of the matrix. A numerical model was developed based on a fully implicit finite difference method. For validating the present model, experiments were conducted with theophylline (THP) as the model drug in 0.1 M phosphate buffer at pH 7.4 and the theoretical values were compared with the obtained data. The effect of different parameters on the release of the drug from the alginate matrix was also evaluated.

Methods

Materials

Medium viscosity sodium alginate powder (viscosity of 2% solution, 25 °C ≈ 3500 cps, Sigma-Aldrich, London), calcium chloride dihydrate (Merck, Germany), theophylline anhydrous with a purity ≥ 99% (Sigma-Aldrich Chemicals Ltd, USA) were used. All other chemicals used were of analytical grade and were procured locally.

Methods

Preparation of drug-loaded calcium alginate nanoparticles

THP-loaded calcium alginate (Ca-ALG) was synthesized by an ionotropic gelation technique by following a previously reported procedure with slight modification [30, 31]. Aqueous sodium alginate solution (1 %, w/v) was mixed together with honey (added as surfactant and stabilizer). THP was dispersed in the solution at the ratio of 20% (w/w) (compared to the weight of Ca-ALG). Aqueous calcium chloride solution (1 %, w/v) was added drop-wise into this solution with constant stirring by a magnetic stirrer. This homogenized mixture was sonicated for 5 min. Nanoparticles were collected via centrifugation at 3500 rpm for 5 min, washed, and finally dried under vacuum.

Swelling studies

The swelling nature of nanoparticles was established by a tea bag technique [32, 33]. A known quantity of dried sample (W_d) was taken in a pre-weighed tea bag (mixed cellulose ester (MCE) membrane of 25 nm pore size, Millipore) and permitted to swell in a solution of 0.1 M phosphate buffer of pH 7.4 for a particular duration. The swollen samples were withdrawn and weighed instantly after evacuating the excess liquid from the surface with a filter paper (W_s). The swelling percentage was computed using Eq. (1). Each swelling study was performed three times and the average value obtained.

$$S = \left[\frac{Ws - Wd}{Wd}\right] \times 100 \tag{1}$$

In vitro drug release studies

In vitro drug release studies were carried out in 0.1 M phosphate buffer, pH 7.4, as per the United States Pharmacopoeia standard (37 °C, 100 rpm) [34]. THP concentration was detected using a UV–Vis spectrophotometer (PerkinElmer Lambda Bio 40) at 286 nm [27]. All experiments were conducted in triplicate.

Mathematical analysis

Release mechanism Upon contact with simulated fluids, the matrix swells and drug release from the swollen matrix is governed by

1. Advective transport of drug
2. Molecular diffusion
3. Hydrodynamic dispersion within the system

Model assumptions To derive the governing equation of transport, the following assumptions are made regarding drug release from the alginate matrix system.

1. Upon contact with release medium, hydrodynamic dispersion occurs.
2. Matrix swelling is isotropic, ideal, and uniform throughout the device.
3. Perfect sink conditions were kept throughout the study.
4. The dispersion of the drug is uniform within the polymer matrix.
5. No mass loss takes place during the entire process.

It was assumed that the drug diffuses out of the domain in only one dimension. Therefore, the drug transport process in the entire system can be portrayed by the one-dimensional equation. The governing transport equation of drug release in the system is derived based

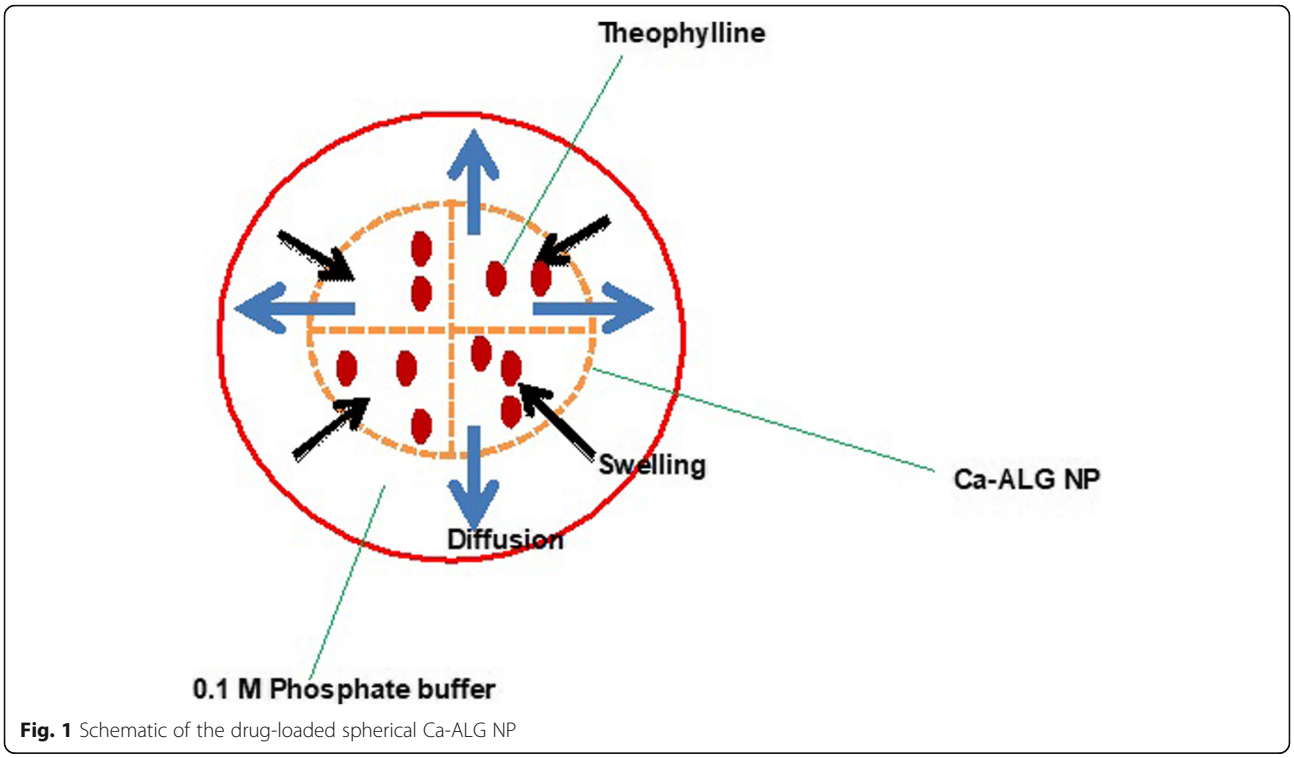

Fig. 1 Schematic of the drug-loaded spherical Ca-ALG NP

on the principle of conservation of mass for an element in the system and is given as

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} - v\frac{\partial C}{\partial x} \tag{2}$$

where C is the concentration of drug in the system ($M\,L^{-3}$), D is the hydrodynamic dispersion coefficient ($L^2\,T^{-1}$), v is the average velocity ($L\,T^{-1}$), t is time, and x is the distance along the axis. The drug diffusion coefficient D can be found experimentally by the reported method [35–37]. Although the velocity may be varying with respect to space and time, in this work the velocity across the entire system is assumed constant and equal to its vertically averaged magnitude. Figure 1 represents the schematic of the drug-loaded spherical calcium alginate nanoparticles (Ca-ALG NP) for mathematical analysis.

The initial and boundary conditions to the problem can be stated as follows:

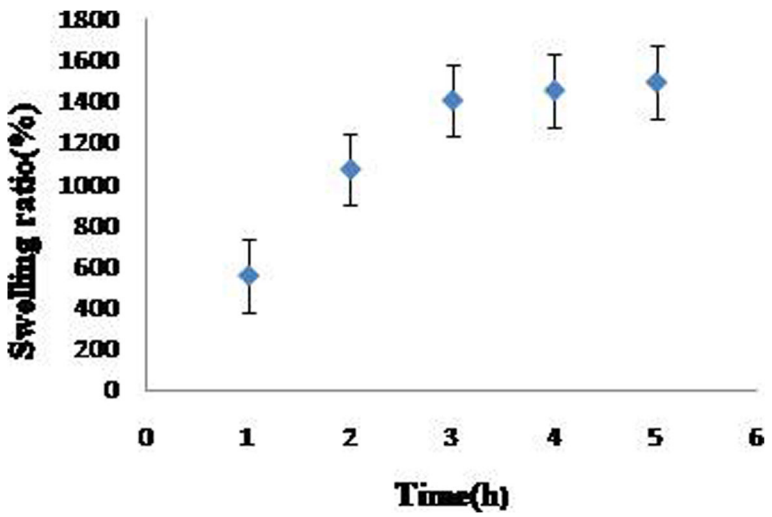

Fig. 2 Swelling kinetics of Ca-ALG NP exposed to phosphate buffer (pH 7.4)

$$t = 0; C = 0 \quad (3)$$

Initially, the drug concentration at the surface of the matrix is supposed to be equal to zero.

$$C(0,\ t_1) = C_{\max} \quad (4)$$

$$C(x, t_1) = 0 \quad (5)$$

$$C(x, t_\infty) = C_{max} \quad (6)$$

Equation (4) corresponds to the inlet boundary condition, which represents the concentration of the drug at the point of release. Equation (5) represents the outlet boundary condition in the system and Eq. (6) implies that after a particular time maximum drug release is achieved and it remains constant in the system.

Numerical model

The source code of the numerical model for simulating the drug release was written in MATLAB. The drug transport equations were discretized using a fully implicit numerical scheme of a finite difference method. An upwind implicit scheme was utilized for discretizing the advection part in Eq. (2) whereas a fully implicit scheme was used for discretizing the diffusion part in Eq. (2). Thomas algorithm was employed for solving the resulting set of simultaneous linear algebraic equations. The continuity of fluxes at the drug-matrix interface was ensured by iterating the solution at each time step. A uniform grid size was selected along the axis; finer grids were selected in the matrix whereas relatively larger grid sizes were adopted in the medium. The concentration flux transfer through the drug-matrix interface was accurately modelled by keeping a relatively small grid size at the interface. The validation of the numerical model was done by comparing the numerical model results with the experimentally obtained values.

Results and discussion

Swelling studies

ALG is composed of β-d-mannuronic acid (M) and α-l-guluronic acid (G) units and has the ability to bind divalent cations like Ca^{2+}, leading to the formation of junction zones. The swelling nature of ALG nanoparticles was evaluated in the simulated intestinal fluid of pH 7.4 at room temperature (Fig. 2). The kinetics and mechanism of drug release was greatly dependant on the swelling nature of the drug carrier. The nanoparticles exhibited a remarkable swelling in the simulated intestinal fluid. At this pH, which is above its pKa value (pKa of ALG = 3.5), all the carboxylate groups of ALG are ionized and increase the electrostatic repulsion between ions. In addition, an ion-exchange process occurs between the Ca^{2+} ions present in the "egg box" cavity of polyguluronate blocks of ALG and Na^{+} ions of simulated intestinal fluid, which causes an increase in electrostatic repulsions among negatively charged carboxyl groups. Both the effects enhance the anionic density and the hydrophilicity of the polymer and cause a pronounced swelling and relaxation of the chains. After 3 h, the matrix achieved its maximum swelling. As a result, the volume of the system is changed and causes an increase in mobility and drug diffusivity.

Drug release studies

ALG nanoparticles contain numerous pores. Upon contact with the simulated intestinal fluid, these pores were filled and a part of drug transport occurs by diffusion.

Solubility of THP in water is 8.3 mg/ml [38]. The high hydrophilic nature of the ALG matrix ensures that the drug is present in the dissolved form on contact with

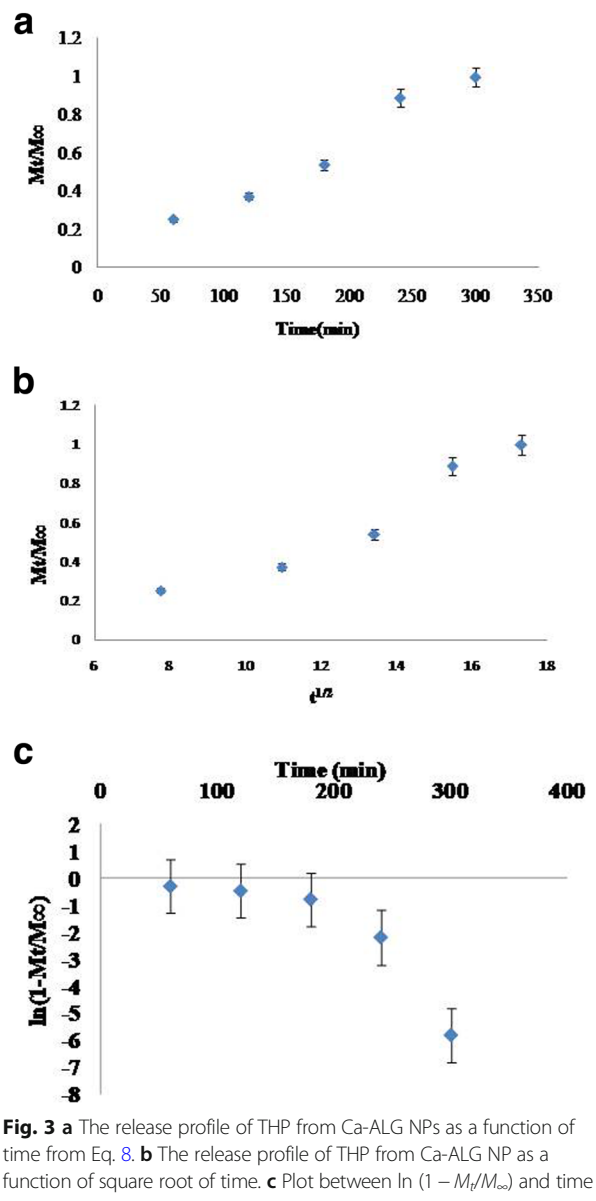

Fig. 3 **a** The release profile of THP from Ca-ALG NPs as a function of time from Eq. 8. **b** The release profile of THP from Ca-ALG NP as a function of square root of time. **c** Plot between ln $(1 - M_t/M_\infty)$ and time

the simulated biological fluid. The percentage of swelling of ALG in the first 1 h was found to be 600. Since the maximum drug loading is 60%, the concentration of the drug in the matrix is much lower than its solubility upon swelling. Hence, drug dissolution is not considered for the formulation of the mathematical model.

Determination of diffusion coefficient

For one-dimensional radial release from a sphere of radius r, with a constant drug diffusion coefficient D, under a perfect sink condition, the drug release can be expressed by Flick's second law [39, 40] and the solution can be written as

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2} \exp\left[\frac{-D\pi^2 t}{r^2}\right] \tag{7}$$

For short time behavior

$$\frac{M_t}{M_\infty} = 6\left[\frac{Dt}{\pi r^2}\right]^{\frac{1}{2}} \tag{8}$$

where (M_t/M_∞) is the fractional release and M_t and M_∞ are drugs released at time "t" and at equilibrium respectively.

The initial diffusion coefficient D_i and average diffusion coefficient D_A can be calculated from a plot between (M_t/M_∞) and $t^{1/2}$ (Fig. 3b).

For calculating D_i, the portion of profile up to $(M_t/M_\infty) < 0.6$ was analyzed, and for calculating D_A, the entire portion of the profile $0 < (M_t/M_\infty) < 1.0$ was considered [36].

The late diffusion coefficient D_L can be calculated from the plot between ln $(1 - M_t/M_\infty)$ and t (Fig 3c) [37].

The values of D_i, D_A, and D_L were calculated as 15.8×10^{-2} cm^2/min, 22.3×10^{-2} cm^2/min, and 2.1×10^{-2} cm^2/min respectively. While comparing these values, it was found that D_A possesses a higher value than D_i and D_L. The smaller D_L value indicates the slow penetration of water into the polymeric matrix during the late stage. However, the value of D_A exactly reflects the changes in the diffusivity during the entire drug release; only the D_A was considered for further calculation.

The experimental release profile from the THP-loaded Ca-ALG nanoparticles is shown in Fig. 3.

Validation of experimental and theoretical results

Using the theoretical model, drug release was predicted with and without considering swelling, and the comparison is given in Fig. 4 which shows that the experimental value fits well with the theoretical value predicted based on diffusion. However, after 3 h, a deviation was observed for experimental value from the theoretical value calculated considering the diffusion with swelling process. This can be explained by the swelling profile of Ca-ALG NP as shown in Fig. 2. Maximum swelling was achieved in 3 h and after which the entire drug release was via diffusional transport from the fully swollen hydrogel. The D_L value also supports this observation.

Conclusions

A mathematical model was developed to depict the drug release from alginate matrix, by considering the Fickian diffusion of the drug from spherical nanoparticles and swelling using THP as the model drug. The initial, average, and late diffusion coefficients were calculated, and average diffusion coefficients were used for

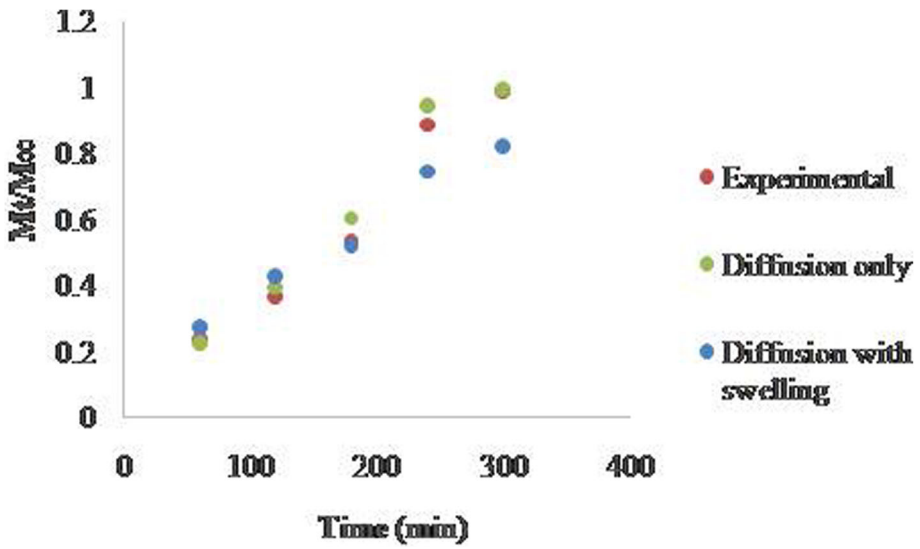

Fig. 4. The validity of the model: predicted with diffusion only, diffusion with swelling, and experimentally determined relative amount of THP release from Ca-ALG NP versus time [release medium: phosphate buffer (pH 7.4)]

further calculation. The theoretical drug release values were validated with experimental values by considering diffusion and diffusion with swelling. It was found that after 3 h, the drug release from fully swollen spherical nanoparticles was purely diffusional transport. The numerical model was found to be sufficiently accurate in predicting the drug release from the alginate matrix. The developed model could be extended for quantitative prediction of drug release from hydrophilic spherical matrices.

Abbrevations

ALG: Alginate; Ca-ALG: Calcium alginate; Ca-ALG NP: Calcium alginate nanoparticles; MCE: Mixed cellulose esters; THP: Theophylline

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Authors' contributions

DT carried out the experimental studies and drafted the manuscript. VV carried out the theoretical modelling studies. KK helped to design the studies, and MS conceived of the study, participated in its design and coordination, and helped to draft the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials

Data will not be shared because it contains unpublished data.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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