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In vitro drug release rates from asymmetric-membrane tablet coatings: Prediction of phase-inversion dynamics

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Abstract

Most of the controlled-release systems developed for drug delivery applications depend on membrane technology. The dense structure of some membranes used in controlled-release systems can excessively prolong the release of drug due to the low permeability of the coating to drug. To increase the drug release rate, asymmetric-membrane tablet coatings were prepared by a phase-inversion technique using cellulose acetate/acetone/water solution. The roles of the composition of the membrane solution and the evaporation condition on the release rate of drug were determined using in vitro dissolution and morphological studies and predicted phase diagrams. Results show that drug release from asymmetric-membrane based tablet coatings is primarily governed by the dynamics of the phase-inversion process with zero-order or near-zero-order release easily achievable. In an attempt to derive an empirical expression for the release rate of drug as a function of composition of the coating solution, a statistical experimental design was used. Good fit of the experimental data by the empirical expression was obtained. In addition, the predictive capability of the model equation was also found to be satisfactory. Analysis of the significance of each term in the expression indicates that the cellulose acetate:acetone ratio has the most significant influence on the release rate of theophylline.

Keywords: Asymmetric-membrane; Phase-inversion; Statistical design; Cellulose acetate; Theophylline

1. Introduction

Different controlled-release systems were developed for drug delivery applications to maintain a drug level in the body within a specificed therapeutic window. This usually implies achieving prolonged, zero-order release rate over the desired duration of drug delivery. Many controlled-release systems in pharmaceutical industry rely on membrane technology in which a drug-containing core is surrounded by a membrane, and the release rate of the drug is controlled by its diffusion through the membrane [1–5]. In addition to diffusional release, osmotic pumping mechanisms contribute to the total drug release rate, if either the drug is highly soluble or an osmotic agent is added to the active core [6–8]. The membrane coating used in conventional devices usually has a dense structure with a hole drilled through the coating through which the drug is delivered. In some cases, drug delivery ports are formed by adding leachable materials to the coating [9,10]. The release kinetics from dense membrane coated drug delivery systems is controlled by: (1) the concentration difference and/or osmotic pressure difference across the membrane; (2) the permeability of the membrane to water and drug; (3) the thickness of the membrane. The main problem with these systems, in the absence of a hole, is an excessively prolonged drug release due to the low drug permeability of the coating. In an effort to increase the permeability of the coating, plasticizers and water-soluble additives were incorporated in the membrane forming solution and multilayer composite coatings were prepared [9,11,12]. Recently, the advantage of using asymmetric-membrane capsules for osmotic and transdermal delivery of drugs was illustrated by different research groups [6–8,13–17]. Compared to other conventional osmotic delivery devices, the permeabilities and the release rates of the asymmetric-membrane capsules/tablets were determined to be higher [6,7]. The structure of this type of membrane is characterized by a relatively thin, dense skin layer supported on a highly permeable, thicker and porous sublayer that provides mechanical strength and durability [8]. Herbig et al. [6] have shown that the outer surface of the asymmetric-membrane coatings is a key factor to control the drug release rates.

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Asymmetric-membranes are usually made by a phase-inversion technique in which an initially homogenous polymer solution is transformed to a porous, solidified structure by different external effects, such as thermal quenching or exposure to a nonsolvent bath. The morphology of the resulting membrane structure that controls the rate of drug release is strongly influenced by the phase-inversion dynamics. Thus, the ability to formulate efficient drug delivery systems based on the asymmetric-membrane coatings requires a detailed study of the effect of phase-inversion dynamics on the morphology of the membrane and the drug release behavior.

The goal of the studies in this paper is to demonstrate the relationship among the membrane preparation conditions, the resulting morphology and the drug release properties of the membranes. To achieve this goal, the in vitro release of a model compound, theophylline, from asymmetric-membrane tablet coatings is determined, and the morphology of the coatings is examined. In addition, the dynamics of the phase-inversion is quantified in terms of ternary phase diagrams coupled with composition paths determined from a mathematical model developed previously by our group [18]. To draw meaningful and objective conclusions from experimental data and derive an empirical expression for the release rate of drug, compositions of the coating solution are chosen using statistical experimental design.

2. Materials and method

Tablet cores were prepared by compressing the drug without any excipient using a hydraulic press operated at 110 MPa. Stainless steel die with a diameter of 1.2 cm was used to produce 400 mg drug tablet cores. The model drug theophylline was supplied by Eczacibasi A.S. Asymmetric-membrane tablet coatings were applied using a dip coating process (Dip Coater Nima, type: D1L, serial no.: 327). Coating solutions were prepared by dissolving cellulose acetate (Aldrich) in a solution of acetone (Merck) and water. To eliminate variations in final coating thicknesses, the rate of withdrawal of the tablets from the solution was adjusted. Immediately after coating, tablets were rotated for even distribution of the viscous membrane solution, transferred into an environmental chamber (Angelantoni Industries, Italy, Challenge Series, model number: CH250) and kept there for 2 h to allow for evaporation of both the solvent (acetone) and nonsolvent (water). The temperature and relative humidity of air in the environmental chamber was adjusted as 25 °C and 50%, respectively. Tablets were allowed to dry further for a minimum of 24 h at room temperature prior to dissolution experiments. The release rate of theophylline from the tablets was determined by the United States Pharmacopeia (USP) XXIII dissolution methodology (rotating paddles, 50 rev./min; temperature, 37 °C; dissolution medium, 900 ml) using a dissolution tester (Caleva 10ST). To simulate the actual dissolution environment in the body, the pH of the dissolution medium was kept at 3 during the first 3.5 h by adding 8.5 vol.% phosphoric acid to 900 ml distilled water and then increased to 7.4 by adding 5.3 M NaOH to the dissolution medium and kept at this value until the end of the dissolution test. To determine the quantity of drug released from the tablets, samples were taken periodically and assayed by UV spectrophotometry (Shimadzu UV-1601) at a wavelength of 272 nm. Dissolution experiments were performed on three tablets and the release profiles were reported as the arithmetic average of the three experimental runs. Morphology of the membranes was examined using scanning electron microscope (SEM) (Philips, XL-30SFEG). Samples were coated with gold palladium using a Magnetron Sputter Coating Instrument. The thickness of the dense skin layer, the overall porosity, and the average pore size were determined from image analysis of micrographs showing cross sections of the membranes.

3. Statistical design of experiments

To determine the influence of the composition of the coating solution on the release rate of drug, experiments were statistically designed using a commercial software package called Design-Expert [19]. The system studied in this paper consists of three components with compositional restrictions as shown in Eq. (1) below:

$$5 \le \omega_1 \le 15, \qquad 70 \le \omega_2 \le 90, \qquad 5 \le \omega_3 \le 15 \tag{1}$$

where ω_i is the wt.% of component i and 1–3 represent cellulose acetate, acetone, and water, respectively. Any composition outside these limits will probably fail to produce a successful asymmetric-membrane coating. In mixture experiments, the factors are the compositions of the mixture components, and the sum of the fractions of all components is equal to one. Therefore, the factor levels are mutually dependent. Thus, factorial experimental designs are not suitable for response surface modeling of mixtures since such designs require that the experimental treatment combinations be determined by independent adjustments of each component level. In addition, a standard response surface design cannot be used either due to the same constraints. Consequently, using the constraint levels shown in Eq. (1), a D-optimal design was generated by Design-Expert software package. The 14 experimental formulations determined are shown in Table 1. The lower and upper limits on the weight fraction of each component are required to: (a) obtain appropriate viscosity of the solution and coat the tablets uniformly and (b) induce phase separation, thus, forming a porous membrane structure. These constraints were established based on preliminary dissolution experiments, available literature data and the simulation results reported by Altinkaya and Ozbas [18].

Of the 14 formulations listed in Table 1, six experimental runs were required to fit the quadratic mixture model, four additional distinct runs were used to check for the lack of fit and finally four runs were replicated to provide an estimate of pure error. Design-Expert used the vertices, the edge centers, the overall centroid and one point located halfway between the overall centroid and one of the edge centers as candidate points. Additionally, four vertices of the design region were used as check points [19].