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Development of a simple method for the preparation of a silica gel based controlled delivery system with a high drug content

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Abstract

Silica gel was used as core particles to design a simple preparation for controlled delivery system with a high drug content. Drug loading was carried out by immersing the silica gel in a pre-heated drug solution or suspension. HPLC, SEM, DSC, PXRD analysis and N_2 adsorption studies evaluated the drug-loading process. In the next step, the drug-loaded silica gel was coated with hydroxypropyl methylcellulose (HPMC) and an aqueous dispersion of ethylcellulose (Aquacoat®) to control the drug release. The release profile was determined using a dissolution test. The results showed that silica gel could adsorb great quantities of the drug, up to about 450 mg/g, by repetition of the loading process. Evaluation of the drug-loading process indicates that drug deposition in the pores occurs during the loading process and the drug-loading efficacy is strongly related to the drug solubility. On the other hand, the dissolution test showed that the drug release could be controlled by polymer coating the drug-loaded silica gel. An HPMC undercoating effectively suppresses the drug release, as it smoothes the drug-loaded core surface and aids in the formation of a continuous Aquacoat® coating film. The floating property was also observed during the dissolution test.

Keywords: Coating; Controlled release; Pore; Silica gel; Theophylline

1. Introduction

The multi-particulate form offers many advantages over other modified release dosage forms, as it provides less inter- and intra-subject variability and a better statistical assurance of drug release (Rao and Muthy, 2002). Coating the drug-loaded core particles with a polymer film is one of the most widely investigated technologies to make multi-particulate dosage forms. A variety of materials have been applied as core particles for this technology. In practice, Nonpareil® sugar beads and Celphere® crystalline cellulose (Nakano and Yuasa, 2001) are commonly used as the core particles, and a fluidized bed or centrifuge granulator is employed for drug loading. However, the drug-loading ratio is relatively low, since the loading area is limited to the outer surface of core particles. For the high dose formulations, other technologies like extrusion spheronization technology are widely used (Pėrez and Rabiškov¯a, 2002; Bashaiwoldu et al., 2004), though this technology usually requires many manufacturing processes (Williams and Liu, 2000) and higher production costs.

To overcome these pharmaceutical difficulties, there has been increasing interest in the use of porous materials as the drug-loading core by making use of their high surface area. One of the well-known applications is incorporating a drug into a silica gel matrix during polycondensation of an organic silicate, which is known as the sol–gel process (Ahola et al., 2000; Kortesuo et al., 2000, 2001). However, depending on the conditions of the polymerization process such as pH-value, temperature, organic silicate, additive, etc., the release rate of the drug from the porous silica particles is strongly

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influenced. Thus, the production of such formulations with a reproducible release pattern is complicated. Furthermore, not all the drugs can be used because they will be decomposed under the conditions used for particle production. Another known method is porous silica gel are stirred in excess drug solution or suspension. Chen et al. (2004) prepared drug-loaded silica gel by stirring drug and silica gel solution for over 30 h, rinsing unentrapped drug with acetone and succeeding vacuum process for 3 h. Otsuka et al. (2000) reported the similar drug-loading process. They stirred drug and silica gel in chloroform for 6 h and evaporated the obtained mixture under reduced pressure. The obtained powders were dried in vacuo for 3 h. In these drug-loading processes, drug and silica gel suspension were agitated for more than several hours and the obtained silica gel should be dried under vacuum conditions for additional hours. Besides not all the drug in the drug solution is entrapped in this process, some unentrapped drug remains in the solution or suspension.

Compared to these known methods, a new method we have designed in this study is a simple method. A silica gel was immersed in a drug solution or suspension followed by drying them in a conventional tray drier. Instead of using excess medium, requisite minimum drug solution or suspension were loaded. All the drug solution was adsorbed in silica gel instantly in the immersion process and stirring process was not needed. Therefore, the vacuum process was not essential and a high yield could be achieved. Furthermore, this method can be applied to a variety of drugs, since the decomposition observed in the sol–gel process is difficult to occur.

In addition to the manufacturing process, the effect of the pore diameter of silica gel and drug solubility on the drug-loading process was investigated in this paper. The drug release properties of various coating formulations were evaluated in vitro by means of a dissolution test. The floating behavior of the coated particles observed during the dissolution test was also studied.

2. Materials and methods

2.1. Materials

Theophylline anhydrous (Tokyo Kasei Kogyo Co. Ltd., Tokyo, Japan) was used as a model drug and two types of porous silica gel sample, C10 and C50 (supplied by Fuji Silysia Chemical Ltd., Aichi, Japan), were used for the silica gel core. The particle size, pore volume, pore diameter and specific surface area of the silica gel core are listed in Table 1. These data are cited from the sample catalogue and certificate of analysis. An aqueous dispersion of 30% ethylcellulose (Aquacoat®, Asahi Kasei Corporation, Osaka, Japan) and hydroxypropyl methylcellulose (HPMC TC-5, Shin-Etsu Chemical Co. Ltd., Tokyo, Japan) were used as the coating materials. Triethyl citrate (TEC CITROFLEX 2, Morimura Bros., Inc., Tokyo, Japan) and polyethylene glycol 6000 (PEG 6000, NOF Corporation, Tokyo, Japan) were added as plasticizers to the coating formulations.

Table 1
Surface geometric structure of silica gel used as silica gel core

Sample name	Particle size (mm)	Pore volume (mL/g)	Pore diameter (nm)	Specific surface area (m^2/g)
C10	0.85–1.7	1.0	10	300
C50	0.85–1.7	1.0	50	80

Data are cited from the sample catalogue and certificate of analysis.

2.2. Preparation of drug-loaded silica gel

Between 2 and 64 g of theophylline was added to 100 mL of water or ethanol and heated at 80 °C in order to achieve a better solubility. Water and ethanol were agitated over a hot plate stirrer and theophylline was added when the medium reached approximately 80 °C. Amount of theophylline added until precipitation of drug appeared was used to determine the solubility. The solubility to water was 160 mg/mL and that to ethanol was 25 mg/mL, respectively. Thus, an aqueous solution and ethanol suspension were obtained when the drug concentration was higher than 25 mg/mL. In the next step, 100 g of dry silica gel were immersed in the theophylline solution or suspension. The dry silica gel used in this study is impregnated with 1.3 mL of water and 1.6 mL of ethanol per 1 g; therefore, all of the drug solution was immediately adsorbed into the silica gel pores in this step, and the drug-loaded silica gel has dried already at this step. In the last step, the silica gel was placed on a tray drier overnight at 80 °C to remove the residual water or ethanol from the internal pores.

2.3. Coating procedure

Two types of coating solutions were prepared by mixing suitable amounts of coating materials, plasticizers and water with a propeller mixer. The first was a 10% HPMC/PEG 6000 solution and the other was a 20% Aquacoat®/triethyl citrate suspension. The ratio of polymer/plasticizer is 4:1 in both coating formulations. The HPMC coating was used as an undercoating of the Aquacoat® overcoating. In the coating process, 35 g of theophylline-loaded silica gel was placed in the coating chamber of a fluid bed granulator (FLOW COATER MINI, Freund Industrial Co. Ltd., Tokyo, Japan) and fluidized to equilibrate the temperature at 60 °C. Both the HPMC coating solution and Aquacoat® coating suspension were atomized by 1.0×10^{-4} kg f/m^2, and the spray rate was controlled between 1 and 2 mL/min. The coated silica gel was dried in the bed for 10 min between the HPMC undercoating and Aquacoat® overcoating. The duration of the coating process depends on the coating ratio. For a maximum coating, the total volume of the atomized coating solution/suspension was 47.5 mL, and it took approximately 30 min to finish the coating. After the coating, the coated silica gel was evenly distributed in a sample tray, and then cured on a tray drier at 80 °C for 1 h. The curing condition was kept constant,