INTRODUCTION

A variety of approaches are available for developing prolonged-release oral dosage forms. Such approaches include the use of polymers as fillers or coatings to prepare tablets, capsules, pellets, matrices (swellable or erodible), and the like.[1-3] The choice of method for achieving controlled release in a particular application depends on a number of factors such as the cost, potency, properties of the agent, and environment of use. In monolithic matrix systems, the agent is generally dispersed or dissolved throughout the excipient. There are several methods for preparing controlled-release matrix tablets such as by direct compression, wet granulation, and slugging. The direct-compression method is the most convenient for preparing controlled-release dosage forms of matrix tablets. The successful application of the direct compression method in preparing matrix types of controlled-release dosage forms depends on the selection of suitable matrix materials.[4,5] Among the reported matrix materials, various viscosity grades of hydroxypropyl methylcellulose (HPMC) and their chemically modified derivatives are the most popular choices.[6-8] However, granulation is usually necessary to improve the flowability when HPMC is used as the matrix material especially when a high-speed tabletting machine is used.

Using the aqueous dispersion of ethylcellulose or other polymers in different media as a granulating agent for drugs or drug/excipient mixtures to retard drug release has been extensively tried.[9-11] Most studies examined the sustained-release ability of a drug or drug-excipient mixture by granulating these polymers. Nevertheless, lactose and dicalcium phosphate have seldom been reported as being used for direct compression excipients of controlled-release matrix tablets, although lactose and dicalcium phosphate are commonly used as excipients for conventional solid pharmaceutical forms, not only because they are chemically inert but also because they are economical to use.[12,13] In previous studies, these 2 commonly used excipients for traditional dosage forms were granulated with an aqueous dispersion of ethylcellulose which was applied to test their ability to control drug release as a direct-compressible excipient.[14-15] In both studies, results demonstrated that the use of ethylcellulose as the granulating material might introduce a more-hydrophobic nature to the excipients by partially coating or fitting into the interstitial structure of granules. As a result, their sustained/controlled-release properties both in vitro and in vivo were suitable as a matrix type of controlled-release dosage form for the water-soluble drug captopril. In this study, the influence of different drug solubility characteristics on the release properties of this matrix system was studied. Nifedipine, a poorly water-soluble drug which requires the assistance of a solubilizer to improve the solubility for better control of the release characteristics, was selected as the model drug.

MATERIALS AND METHODS

Materials

Nifedipine was purchased from Sunlite Chemical (lot no. 7154) (Japan). Lactose was supplied by DMV (Veghel, the Netherlands). Surelease® (a 25% aqueous dispersion of ethylcellulose) was obtained from Colorcon (Bexley, UK). Hydroxypropyl methylcellulose (Metolose 60-SH, 50 cps) was from Shin-Etsu (Tokyo, Japan). Hydroxypropyl methylcellulose (HPMC, 5 cps) was supplied by Dow Chemical (USA). Dicalcium phosphate was from BK Ladenburg (Germany). Polyvinylpyrrolidone (PVP, K30) was provided by BASF Aktiengesellschaft (Germany). Tween 80, sodium chloride, hydrogen chloride, and acetone were supplied by Merck (Germany).

Preparation and Characterization of Granulated Excipients

Four hundred grams of either lactose or dicalcium phosphate was mixed with or without hydroxypropyl methylcellulose (HPMC, 50 cps) in a planetary mixer (Kitchen-Aid, model K45SS) at 140 rpm for 5 min. The ethylcellulose aqueous solution, obtained as Surelease® and adjusted correspondingly to either 50 or 90 g in total water weight for lactose and dicalcium phosphate formulations, respectively, was slowly poured into the above mixtures. The wet slurry was stirred at 250 rpm for 5 min and passed through a 30-mesh screen by hand. The granulated excipient was dried in a forced-air convection oven at 60 °C for 24 h. The dried granules were passed through a 20-