to different extents.[8,9]

In general, processing times of coatings are sometimes not long enough and temperatures not high enough to plasticize the coating material to form a controlled membrane with an acceptable integrity. As a result, curing by subjecting products to higher temperatures for longer time periods is necessary to accomplish the purpose. By this way, the release of drugs from membrane-controlled pellets become reproducible throughout the storage period.

The preparation of pellets in as dense a form as possible is beneficial to their application as a controlled-release dosage form. A denser structure is especially critical for pellets containing a large amount of a drug. Pellets prepared by an extrusion and spheronization process have a denser structure, resulting in prolonged release of drug from the pellets.[6-7,10] This makes the integrated process of extrusion and spheronization a desired method for producing pellets with a high drug content for purposes of prolonged drug release.

In a preliminary study, it was concluded that the treatment of etofibrate powder by melting was capable of improving the density of the powder, and the spheronization of pellets positively increased pellet density. With partial melting or softening of the drug chemicals at an elevated temperature, spheronization at this temperature not only increases the density of the structure of the pellet, but also allows the controlled-release membrane to be cured more evenly. Therefore, it was thought that curing pellets with spheronization at an elevated temperature after membrane coating of pellets would have a synergistic effect on the increase of pellet density as well as the prolongation of drug release.

MATERIALS AND METHODS

Materials

Etofibrate was selected as a model drug (Geyer GMBH &CO. KG., Germany). Polyethylene glycol 6000 and acetone were purchased from Merck Company (Germany). Surelease® (ethylcellulose aqueous latex, Colorcon Ltd, UK) was used as the film coating polymer. Talc was obtained from Wei-Ming Pharmaceuticals (Taipei, Taiwan).

Preparation of Etofibrate Pellets

Etofibrate powder (200 g) was wet massed with a water solution containing 10 g PEG 6000 and 10 g acetone in a planetary mixer and continuously blended for 30 min. The wet mass was immediately extruded with a cylinder-type extruder (model CY-WG-8, Chuan Yung Industrial, Taipei, Taiwan) with a 1.0 mm orifice screen. The resultant extrudates were placed on the 23 cm diameter cross-hatched plate of the spheronizer (model SY-5, Shang Yuh Machine, Taipei, Taiwan). The spheronization speed was fixed at 960 rpm, and the residence time was 10 min. After spheronization, pellets were dried in a hot-air oven at 40 °C for 10 h.

Film Coating of Etofibrate Pellets

A charge of 400 g of etofibrate pellets was placed into the chamber of a fluidized-bed granulator and coater (Model GPCG-1, Glatt Air Techniques, Germany) and fluidized by opening the inlet air flap. A film dispersion was prepared by mixing Surelease® latex with talc in an amount of 50% w/w of polymer, and then the final solid content was adjusted to 12.5% w/w by dilution with deionized water. When the outlet temperature reached 37 °C, the dispersion of the film polymer was bottom-sprayed onto the fluidized etofibrate pellets from an atomizing nozzle (1 mm) attached to a peristaltic pump. During processing, the spraying rate and inlet air temperature were adjusted to maintain the outlet air temperature at 27-30 °C. The spraying continued until the design amount of film polymer (2.5%, 5.0%, and 7.5% of pellet weight) was sprayed. Finally, the film-coated pellets were dried in a hot-air oven for another 10 h at 40 °C after coating.

Pellet Curing

A spheronizer (model SY-5, Shang Yuh Machine, Taiwan) having a jacket wall was used to process the curing spheronization. The jacket temperature was adjusted by a controlled-temperature water bath attached to a water recycling pump. Four jacket temperatures (ambient, 40, 45, and 47.5 °C) were chosen to examine the effects of curing spheronization on pellet properties. When the designated jacket temperature was