嘉南藥理科技大學專題研究計畫成果報告

減肥藥物圓粒控釋劑型之製備及其性質的探討

計畫類別：■個別型計畫　　□整合型計畫

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INTRODUCTION

Obesity is one of the pathologies with ever-increasing prevalence in modern societies. Drug that act through noradrenergic and serotonergic mechanisms have historically served as the mainstays of pharmacologic treatments for obesity. Methylephedrine HCl has competitive alpha 2-adrenoceptor antagonist activity, and may be possibly serve a therapeutic role. Methylephedrine HCl is readily soluble in water, whereas it is subject to gut wall metabolism and thought to be absorbed erratically. It is well known that no digestive enzymes are secreted in the colon. With respect to delivery of drug to the colon to avoid intestinal wall metabolism, natural polysaccharides are now extensively used for development of solid dosage forms as colon-specific drug carrier systems. Chitosan is one of the natural polysaccharides, which was prepared from chitin of crabs and lobsters by N-deacetylation with alkali. It has recently been used in biomedical and pharmaceutical field because of its favorable properties of biodegradability, low toxicity and good biocompatibility. In pharmaceutical applications, it has been designed to act as a direct-compression diluent, a new vehicle or drug carrier for sustained release preparations, as well as a co-grinding diluent for the modification of drug dissolution rate and enhancement of intestinal permeability.

In the development of controlled release dosage forms for oral administration, multiple-unit dosage forms such as pellets are believed to have many advantages compared to single unit dosage forms. For example, predictable concentration / time profiles can be achieved and local mucosa irritations can be avoided.

The purpose of this study was to develop a polymeric controlled-release drug delivery system of methylephedrine HCl as a part of our studies on the pharmaceutical application of chitosan.

MATERIALS AND METHODS

Materials

Methylephedrine HCl was purchased from Sigma Chemical Co. (St. Louis, USA). Lactose was purchased from Avonmore West INC. (St. Idaho, USA). Chitosan was purchased from Aldrich Chemical Co. (Steinheim, Germany). Lactic acid was purchased from E. Merck Co. (Darmstadt, Germany). All other reagents and solvents were of analytical or equivalent grade.

The preparation of pellets

The extrusion-spheronization is one of the valuable methods used to prepare pellets. The formulations used in the experiments are shown in Table 1. Methylephedrine HCl HCl and the binary mixtures of Avicel and lactose as bulk materials were dry mixed thoroughly. After the water or chitosan hydrogel was added as a binding agent, the moistened mass was immediately passed through a 20 mesh sieve. The resulting extrude was then sphered by rotating friction plate. The produced pellets were dried at room temperature.

Release studies

The release of methylephedrine HCl HCl from the prepared pellets was determined over 6 hours, using the USP rotating-basket dissolution method at 150 rpm, 1000 ml of HCl solution (pH=1.2 and 4.5) at 37℃ ±0.5℃ was used as a dissolution medium. An equivalent amount of pellets containing 100 mg of methylephedrine HCl was employed for each dissolution study. At predetermined time intervals, 3 ml samples were withdrawn and replaced with an equal volume of fresh dissolution medium to maintain the original volume. The concentration of

drug in each sample was measured spectrophotometrically at 218 nm. Triplicate runs were carried out for each study.

Differential scanning calorimetry

DSC thermograms were obtained using a Perkin-Elmer DSC-7 differential scanning calorimeter. Sample sizes were in the range of 3-5 mg and were sealed in an aluminum pan. Thermogram were recorded from 50 to 180 ℃ at a heating rate of 10 ℃/min.

RESULTS AND DISCUSSION

Pellets having better spherical geometry and smooth surface were prepared by adding Avicel 101 as a diluent than Avicel 102. With respect to the yield rate by weight, majority of particles added water as a binding agent were larger than 1 mm. However, the particle size was reduced due to addition of chitosan (5 % w/w) hydrogel solution instead of water.

In *in vitro* release of methylephedrine HCl from pellets, the pellet without adding chitosan was found to be rapidly drug release in first 1 h, then slowly release lasting over 12h. Because no important difference in shape of pellets was observed in the dissolution process, thus the kinetic behavior was controlled by diffusion but not degradation. The rate of drug release from the pellets was highly dependent on the solubility of drug in water. Methylephedrine HCl is readily soluble in water, leading to initial releasing drug rapidly. However, the addition of chitosan hydrogel solution instead of water as a binding agent during the granulation seemed to yield slower drug release with the same particle size in pH 1.2 medium. When the opposite charge material, such as sodium lauryl sulfate or gum, was added into the binary mixtures of Avicel and lactose, the chitosan, a

cationic polymer, was reacted with sodium lauryl sulfate to form coacervates. The produced pellets exhibited a delayed action of release as compared with pellets prepared with water or chitosan alone. Moreover, the percentage of drug and chitosan release was much lower in pH 4.5 buffer solution compared with the HCl solution, probably due to the gelation properties of the coacervate at different pH.

Even though hardness/tensile strength of pellets did influence the rate and amount of drug release, the influence of polymer incorporating into chitosan was more important. The effect of copolymer on retarding release of the drug from pellets conformed to the following order: non-ionic polymer (ex: PVA) > anionic polymer > cationic ploymer. To elucidate the influence of chitosan on the mechanism for modulation of methylephedrine HCl release from pellets, differential thermal analysis was utilized to examine the interaction of methylephedrine HCl with excipients in the solid state. There are no significant interaction can be observed among the excipients of pellets except adding sodium lauryl sulfate to form coacervate in the thermogram of pellets. The above results propose the possibility of modifying the formulation by the formation of chitosan-copolymer coacervates to obtain the desired controlled release of drug for a colon-specific delivery system.