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Abstract

PREPARATION AND IN-VITRO EVALUATION OF TIME-CONTROLLED PELLETS OF MATRINE FOR COLON-SPECIFIC DELIVERY

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Time-controlled colon-specific drug delivery system is a new type of drug delivery system based on the fact that the small intestinal transit time is relatively consistent at 3-4 h and irrespective of formulation and dietary factors, which made the drugs do not release in the stomach, duodenum, jejunum, ileum front-end but release in the colon for local or systemic treatment. The model drugs for time-controlled colon-specific delivery pellets are mostly the drugs with the molecule weight higher than 500. However, for the drugs with the molecule weight less than 300 and with good aqueous solubilities, it is very difficult to realize the time-controlled release both in-vitro and in-vivo. Matrine is a hydrophilic active compound with lower molecular weight (< 300) isolated from a commonly used Chinese medicine Radix Sophorae Flavescentis, which showed anti-inflammatory, anti-bacterial, anti-allergic, sedation and immune suppression activities.

In this study, the time-controlled release pellets of Matrine with a layer of rupturable coating and a layer of controlled coating were successfully prepared by fluid bed using a single-factor and central composite design and response surface method for optimization.

The following parts are included in this study:

1. Determination of Matrine by HPLC. After the determination of its UV absorption spectrum, a HPLC method was developed for analysis of Matrine in-vitro. The validation results showed that this established HPLC method was simple, reliable and repeatable.

2. Optimization of fluid bed coating conditions. Amount of loaded pellets, airflow, inlet temperature, spray rate and spray pressure are main fluid bed coating parameters, by which the coating conditions of the coating materials used in preparation of Matrine coated pellets were established. The evaluations of agglomeration rate showed that the optimized coating conditions were suitable for long-time coating with good qualities.

3. Preparation of Matrine time-controlled colon-specific drug delivery pellets by a single-factor study. The single-factor study showed that although the release of drug could be reduced by a single layer coating of Surlease, but no enough lag time could be obtained. While when using HPMC as a swelling layer and Surelease as a time-controlled layer, the coated pellets could not obtain enough lag time (e.g. 5 h) and complete release after 16 h. Therefore, pellets with two layers of coating were prepared by fluid bed. The first layer was composed by the mixture of HPMC and ethylcellulose aqueous dispersion (Surelease) as the swelling and controlled release layer. The outer layer of the pellet was coated with Surelease as the time-controlled film. The optimized condition to prepare the pellets with 3-8 h delayed release is as follows: mass ratio of swelling controlled-release layer (Surelease: HPMC) = 3:1; weight gain of swelling controlled-release layer 50% and weight gain of time-controlled layer from 10% to 30%.

4. Optimization of coating pellets using response surface methodology and statistical analysis using Design-expert®. The three formulation variables studied were the amount of Surelease outer coat, amount of Surelease-HPMC inner coat, and the ratio of Surelease-HPMC inner coat. The two response variables studied were the amount of drug release in 5 h and in 16 h. Thus, the statistical design was based on three factors and two levels. The optimization region was in line with the design goals by the establishment of a quadratic polynomial mathematical model, analysis of variance, the portrayals of the effects of surface maps and contour map by contour lines overlap. In this study, coating pellets release in the line with the principle of double-layer membrane by microscope and scanning electron microscopy study. As mathematic model fitting results suggested, zero order equation could explain the drug release from Matrine delayed release pellets. The coating pellets were chemically stable in accelerated stability experiments in 3 months. However, the lag time of the drug in the pellets significantly reduced during the accelerated stability tests.