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A time-released osmotic pump fabricated by compression-coated method: Formulation screen, mechanism research and pharmacokinetic study

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ABSTRACT

In this investigation, time-released monolithic osmotic pump (TMOP) tablets containing diltiazem hydrochloride (DIL) were prepared on the basis of osmotic pumping mechanism. The developed dosage forms were coated by Kollidon®SR-Polyethylene Glycol (PEG) mixtures via compression-coated technology instead of spray-coating method to form the outer membrane. For more efficient formulation screening, a three-factor five-level central composite design (CCD) was introduced to explore the optimal TMOP formulation during the experiments. The *in vitro* tests showed that the optimized formulation of DIL-loaded TMOP had a lag time of 4 h and a following 20-h drug release at an approximate zero-order rate. Moreover, the release mechanism was proven based on osmotic pressure and its profile could be well simulated by a dynamic equation. After oral administration by beagle dogs, the comparison of parameters with the TMOP tablets and reference preparations show no significant differences for C_{max} (111.56 ± 20.42, 128.38 ± 29.46 ng/ml) and $AUC_{0\text{-}48\ h}$ (1654.97 ± 283.77, 1625.10 ± 313.58 ng h/ml) but show significant differences for T_{max} (13.00 ± 1.16, 4.00 ± 0.82 h). These pharmacokinetic parameters were consistent with the dissolution tests that the TMOP tablets had turned out to prolong the lag time of DIL release.

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1. Introduction

Oral time-released preparations which are designed to release the drug within a proper period of time after a predetermined lag time are developing quickly as more and more extensive application of chronotherapeutics in clinical practice. Several diseases, including arthritis, asthma, allergies, peptic ulcer disease, dyslipidemia and cancer exhibited predictable circadian rhythms [1,2]. In particular, aggravation of cardiovascular diseases like angina, hypertension and myocardial infraction, were more frequent to break out in the early morning before patients wake up [3]. It was badly inconvenient to take the conventional drug dosage providing relief of symptoms and protection from those adverse events when necessary. Consequently, we need the administration of a drug formulated in time-released delivery system, i.e. taken at bedtime with a programmed start of drug release based on circadian rhythms.

There were various approaches for the time-released drug delivery system, such as system based on osmosis, or capsule, system with change in membrane permeability and system with erodible, soluble or rupturable membrane. Now all of them were gaining popularity for prime advantage that drug is released solely when necessity comes. As a result, risks of development of drug resistance, usually seen in conventional and sustained-release formulations, could be reduced. Among the time-released products mentioned above, osmotic pump preparations have stood out, with superiority for not only matching with circadian rhythms, but also exhibiting reliable comparable *in vitro/in vivo* drug release [4,5]. The release rate from these types of system depended on the coating components and the osmotic gap across the membrane, without influences from the pH, peristalsis or other interference in gastrointestinal (GI) tract.

Osmotic pump tablets (OPTs) belonged to the class of rate-controlled systems which provided continuous delivery and different types such as monolithic, two-compartment, two-layer push–pull and three-layer osmotic tablets systems were developed [6]. Theeuwes introduced the monolithic osmotic pump (MOP) and brought forward its basic theory in the 1970s [7,8]. It consisted of an osmotic core coated by a semi-permeable membrane drilled with a delivery orifice. The MOP was very simple to prepare and could release water-soluble drugs at the rate of approximate zero-order [9]. Due to its simple production procedures, the MOP avoiding a sophisticated technique had been an emphasis of recent researches. However, the common osmotic pumps were still facing two technical problems, use of organic solvent for coating outer membrane and drilling process for delivering pharmaceutical ingredients, which extremely limit the industrialization of osmotic pumps in pharmaceutical industry. Although many attempts had been made to resolve these two problems, the current situation of industrialization was still difficult.

With the joint efforts of all explorers, a new face had been put on these matters via microporous membrane and non-solvent coating technology. Recently, osmotic pump tablets had been developed in which the delivery orifice was formed by the addition of water-soluble components in the coating material. Once the tablets came in contact with the GI fluid, the water-soluble component dissolved to forming an osmotic pumping system. Subsequently, water diffused through the microporous membrane to dissolve core components, forming an osmotic gap to control the drug releasing [10,11]. As a consequence, the manufacturing process was simplified with the elimination of drilling orifice. Moreover, compression-coated technology, referred as non-solvent coating method, was employed to the TMOP tablets. Compared with traditional coating method, this new coating technique could avoid disadvantages in the pharmaceutical industrialization, such as environmental pollution accompanying with use of organic solution. In general, the compression-coated tablet was composed of an inner core tablet and an outer coating shell. And its thicker outer shell show inherent advantages for chronotherapeutics because of time taken for penetrating of the membrane i.e. is known as lag time [12]. It was generally accepted that the property of compression-coated tablets was under the influence of the inner core tablet and outer coating shell in the formulation. We had taken the central composite design (CCD) method to determine the interaction of inner core tablet and an outer coating shell for TMOP tablets with optimal formulations. The CCD method which could provide information on direct effects, pair-wise interaction effects, curvilinear variables effects, was suitable for formulation and process optimization in the field of pharmaceutics involving with multiple factors and levels since it was an efficient method to reduce the number of experiments [13–16].

The objective of our investigation is to develop time-released monolithic osmotic pump (TMOP) tablets with microporosity by compression-coated technology, in which involve with neither organic solvent nor drilling process. Diltiazem Hydrochloride (DIL), a calcium channel blocker which inhibits influx of calcium (Ca^{2+}) ions [16], was chosen as the model drug. The DIL is frequently administered orally for the treatment of angina and hypertension as sustained-release formulations to improve compliance, but the constant delivery of DIL into the body also leads to drug resistance or side effects. Moreover, the high water-solubility (>50%, w/v at 25 °C) of DIL are suitable to apply in TMOP preparations. For the compression-coated microporous TMOP tablet, it provided new ideas to both pharmaceutical manufacture and clinical chronotherapeutics.

2. Materials and methods

2.1. Materials

Polyvinylacetate–polyvinylpyrrolidon (Kollidon®SR) is kindly donated by Basf Auxiliary Chemicals Co., Ltd Shanghai, China. Microcrystalline cellulose (MCC, Ph102) was supplied by AsahiKasei. Polyethylene glycol (PEG) was received from Anhui Sunhere Pharmaceutical excipients Co., Ltd. The model drug of DIL, obtained from Shanghai Jinhuan Chemical Co., Ltd, was passed through 100 mesh sieve prior to the experiment. The reference preparation (sustained-release capsule, Herbesser) was purchased from Tianjin Tanabe Seiyaku Co., Ltd.