Design and Evaluation of a Dry Coated Drug Delivery System With Floating–Pulsatile Release

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ABSTRACT: The objective of this work was to develop and evaluate a floating–pulsatile drug delivery system intended for chronopharmacotherapy. Floating–pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release. To overcome limitations of various approaches for imparting buoyancy, we generated the system which consisted of three different parts, a core tablet, containing the active ingredient, an erodible outer shell and a top cover buoyant layer. The dry coated tablet consists in a drug-containing core, coated by a hydrophilic erodible polymer which is responsible for a lag phase in the onset of pulsatile release. The buoyant layer, prepared with Methocel® K4M, Carbopol® 934P and sodium bicarbonate, provides buoyancy to increase the retention of the oral dosage form in the stomach. The effect of the hydrophilic erodible polymer characteristics on the lag time and drug release was investigated. Developed formulations were evaluated for their buoyancy, dissolution and pharmacokinetic, as well gamma-scintigraphically. The results showed that a certain lag time before the drug released generally due to the erosion of the dry coated layer. Floating time was controlled by the quantity and composition of the buoyant layer. Both pharmacokinetic and gamma-scintigraphic data point out the capability of the system of prolonged residence of the tablets in the stomach and releasing drugs after a programmed lag time. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:263–273, 2008

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INTRODUCTION

Chronopharmacotherapy, the drug regime based on circadian rhythm, is recently gaining much attention worldwide. Various diseases like asthma, hypertension, arthritis show circadian variation, that demand time-scheduled drug release for effective drug action for example inflammations associated with morning body stiffness, asthma, and heart attack in early hours of the day.[1] Results of several epidemiological studies demonstrate the elevated risk of different pathologies during a 24-h cycle. Specifically, symptoms of rheumatoid arthritis and osteoarthritis,[2] dyspnoea,[3] and epilepsy appear to have a peak during the night or early in the morning. Ischemic heart diseases, such as angina pectoris and myocardial infarction, are manifested more frequently during these times.[4] Blood pressure which arises notably just before waking up[5] is usually responsible for these attacks. Verapamil hydrochloride

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was chosen as a model drug, for it is a potent calcium-channel blocker and has been effective for preventing the time-related occurrence of ischemia.[6] Verapamil HCl was widely accepted for its anti-hypertension and anti-anginal properties, since it is a calcium antagonist compound. So verapamil HCl is a typical example of drug, which is used in the therapy of symptoms or diseases as described. However, for such cases, conventional drug delivery systems are inappropriate for the delivery of verapamil HCl, as they cannot be administered just before the symptoms are worsened, because during this time the patients are asleep.

To follow this principle one must have to design the dosage form so that it can be given at the convenient time for example bed time for the above mentioned diseases with the drug release in the morning. Using current release technology, it is possible for many drugs oral delivery for a pulsed or pulsatile release, which is defined as the rapid and transient release of a certain amount of drugs within a short time-period immediately after a predetermined off-release period.[7–11] Chronotherapeutical devices based on osmotic pumps have been developed by MaGruder et al.[12] and Cutler et al.[13] A Pulsincap™ system[14] corresponds to a more sophisticated approach while it is composed by a capsule with an insoluble body and a hydrogel plug. Multiphasic drug release was achieved by using a three layer[15] tablet while similar devices were also developed and evaluated in a later stage.[16,17] Time controlled coating systems were also developed by Ueda et al.[18] and Narisawa et al.,[19] including single and multiple unit dosage forms.

The disadvantage of these pulsatile release formulations is that they require a long residence time in the gastrointestinal track. With conventional pulsatile release dosage forms, the highly variable nature of gastric emptying process can result in *in vivo* variability and bioavailability problems. The advantages for gastro-retentive pulsatile dosage forms are also pH dependent drug solubility (in this case verapamil is good example) or better drug bioavailability in stomach, when compared with lower parts of GIT. Overall, these considerations led to the development of oral pulsatile release dosage forms possessing gastric retention capabilities.[20–22] Low density multiparticulate systems for floating–pulsatile release were developed by Sharma et al.[20] and Badve et al.[22] A pulsatile release formulation with the mucoadhesive properties

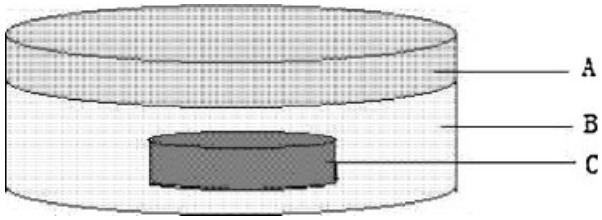

Figure 1. Schematic diagram of the floating–pulsatile release (FPRT) delivery system. A: the layer for buoyancy; B: the layer for drug pulsatile release; C: the rapid-release core tablet.

was developed by Karavas et al.[21] However, at the present time little is known about the *in vivo* performances of the floating–pulsatile release system. More knowledge on the *in vivo* investigation of the system should be useful to devices based on these technologies becoming clinically available.

Objective of this work was to develop and evaluate a pulsatile–floating drug delivery system. The system consists of three different parts, a core tablet, containing the active ingredient, an erodible outer shell, and a top cover buoyant layer (Fig. 1). One layer is for buoyancy and the other for drug pulsatile release. The pulsatile release system with various lag times was prepared by compression with different erodible polymeric layers (press-coated systems) as described previously.[23–25] Combined usage of hydroxypropyl methylcellulose (HPMC) and carbomer in a gastric floating or mucoadhesive drug delivery system has been reported[26,27] to improve the floating properties or mucoadhesiveness of the combined system. Ideally, the novel system could result in (1) a floating dosage form with a prolonged gastric residence time and in (2) a pulsatile dosage form, in which the drug is released rapidly in a time-controlled fashion after rupturing of the coating. Developed formulations were evaluated for buoyancy studies, dissolution studies, gamma-scintigraphic evaluation and pharmacokinetic study.

MATERIALS AND METHODS

Materials

Verapamil hydrochloride (Ver) was purchased from Tianjin Central Pharmaceutical Factory, Tianjin, China. HPMC (Methocel® E5, E15, E50, K4M, Colorcon, UK), ethylcellulose (Ethocel® 45cp, Colorcon, UK), crospovidone (Kollidon® CL,

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