Journal of Drug Delivery Science and Technology 47 (2018) 404–410

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

A specific two-pulse release of rivastigmine using a modified time-controlled delivery system: A proof of concept case study

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ARTICLE INFO

Keywords:
Rivastigmine hydrogen tartrate
Pulsatile release
Compression-coating
Tablet-in-tablet
Dual delivery system
Dissolution test

ABSTRACT

Currently, the orally administrated rivastigmine is based on twice daily formulations which also demand a titration process in order to increase the tolerability of the drug. In the present study an attempt was made to design and prepare an innovative single unit, once daily, double pulse release formulation for oral administration of rivastigmine in order to increase patient compliance without causing tolerance development. The pulsatile system was prepared as a tablet-in-tablet using a compression-coating method. An in-vitro dissolution test was utilized to determine the release profile of the drug from this system. The results showed that the designed delivery system provided two consecutive pulses of rivastigmine with a time difference of 6.5 h between the peaks of the pulses. The outer tablet provided an immediate release which lasted up to 4 h. The inner tablet, on the other hand, which was a film coated tablet, presented a capability of time-controlled delivery which was manifested by a lag time of 3 h followed by a burst release. The lag time was dependent, to a considerable extent, on the film coating weight. Surprisingly, the compression-coating did not alter the release features of the inner tablet whatsoever.

1. Introduction

Dementia is characterized by a severe memory disorder, cognitive disfunction and deterioration of emotional capacities. Alzheimer's disease is the most common cause of dementia [1]. Rivastigmine is indicated for symptomatic treatment of patients with mild to moderately severe Alzheimer's dementia and dementia associated with Parkinson's disease [2,3]. It is a non-competitive, slowly reversible cholinesterase inhibitor, which acts by inhibiting both enzymes: acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) which are responsible for the degradation of acetylcholine. Rivastigmine has a central nervous system selectivity over peripheral inhibition. Gastrointestinal symptoms, such as nausea, vomiting and diarrhea, are the most frequently reported adverse events of the treatment with rivastigmine [2–4].

Rivastigmine is rapidly and completely absorbed with absolute bioavailability of about 40% (3 mg dose) and peak plasma concentrations reaching in approximately 1 h. The elimination half-life is about 1.5 h, with most elimination as metabolites via the urine [3].

Since rivastigmine is classified as an intermediate-acting or pseudo-irreversible agent due to its relatively prolonged inhibition of AChE (of up to 10 h) [3,4] a fast release of the drug formulation is far superior to an extended release. Likewise, due to the fact that the drug administration is accompanied by a titration procedure, in order to increase the tolerability of the drug, the likelihood that an extended release may cause the evolvement of drug tolerance, demanding an increasing dose frequency or dose level [5], should not be underestimated.

Currently, rivastigmine is administrated either orally (as a hard gelatin capsule or solution) providing immediate release or by a transdermal patch formulation presenting an extended release profile [6,7]. The hard gelatin capsule is generally administrated with the effective dose of 3–6 mg twice a day [6].

In attempts to minimize the limitations of the currently existing rivastigmine formulations and maximize the efficacy of the drug, many formulations have recently been developed, including the controlled release formulations [8,9] and the formulations for increasing the bioavailability and brain targeted delivery of rivastigmine [10].

A pulsatile drug delivery system (PDDS) is generally a time-controlled delivery system which is able to release a drug in different doses (pulses) rapidly within a relatively short time period (burst release) with a predetermined off-release (break) period between them [11–15]. PDDS is an efficient way for the delivery of a drug which may exhibit biological tolerance which is a decrease in drug's efficacy upon constant

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https://doi.org/10.1016/j.jddst.2018.08.009
Received 28 April 2018; Received in revised form 25 June 2018; Accepted 9 August 2018
Available online 14 August 2018
1773-2247/

Fig. 1. A schematic illustration demonstrating the cross-section of the tablet-in-tablet dual system, including the outer tablet (OT) and the inner tablet (IT) which is coated by a time-controlling film coating (FC) consisting of calcium pectinate (CaP) particulates and ethylcellulose (EC) as a rigid film forming polymer.

exposure to the drug. Drug tolerance can especially be developed by using the controlled-release or extended release formulations providing a constant drug release [12].

To date, different oral biphasic (dual) delivery systems including tablet-in-tablet and double layer tablets have been developed and evaluated for creating pulsatile release of different active materials [16–19]. However, so far no delivery system has been specifically developed for a pulsatile release of rivastigmine.

The present study was planned to examine a unique release profile of the drug, from an orally administrated formulation, which is entirely different from those provided by the currently marketed products. The main idea was to design a novel, once daily, two-pulse release formulation in order to minimize the adverse effects of rivastigmine and increase patient compliance.

The formulation was based on an innovative single unit dosage form which consisted of a tablet-in-tablet dual system where an inner coated tablet was surrounded by an outer layer (outer tablet) using a compression-coating process (Fig. 1) [20]. Both the inner and outer tablets each contained 3 mg rivastigmine corresponding to 4.8 mg rivastigmine hydrogen tartrate. The unique matrix composition of the outer tablet was formulated to provide the first release pulse as a semi-slow release (fast sustained release) whereas the inner tablet was designed to release the second pulse of the drug in a burst manner following a predetermined lag time. The latter was composed of a unique fast disintegrating core and a novel film-coating combination, providing a certain lag time which was needed to separate two pulses of the drug. The film-coating structure is based on a unique combination of a hydrophobic, rigid film forming polymer such as ethylcellulose and hydrophilic water insoluble particulates such as calcium pectinate (CaP) which are evenly embedded within the film forming polymer. Upon exposure of the inner tablet to the gastrointestinal liquids or any dissolution medium the aqueous solution enters through the particulates, in a controlled manner, into the core creating an increasing osmotic pressure which is concurrently exerted onto the film coat. At a specific point of time, the inner pressure overcomes the strength of the film coat and breaches it. At the same time the core immediately disintegrates, resulting eventually in a fast release of drug [21].

This study aimed to explore the release profile of rivastigmine from the designed dual delivery system with a focus on the effect of the compression coating process on the lag time between two pulses which is provided by the film-coating combination of the inner tablet. Note that, in general, the lag time is defined as the actual time it takes for the burst release to occur (burst time).

2. Materials and methods

2.1. Materials

Rivastigmine hydrogen tartrate was supplied by Novartis (Basel, Switzerland). The excipients used for the preparation of the formulations of both the inner and outer tablets and also for the coating formulation of the inner tablet were purchased from different suppliers as follows: food grades of low methoxyl pectin and calcium pectinate (CaP) powder, containing 4% calcium, from Copenhagen Pectin Kelco (GA, USA), ethylcellulose NF (EC), with different viscosity grades (EC7 and EC20), from Dow Chemical Company (MI, USA), Microcrystalline cellulose (Avicel PH 101) (MCC) from FMC corporation (PA, USA), polyvinylpyrrolidone K-90 and K-30, (PVP K-90 and PVP K-30) (USP grade), and cross polyvinylpyrrolidone, (USP grade) (Crospovidone, CPVP), from BASF (Ludwigshafen, Germany), magnesium stearate (USP grade) from Merck (Darmstadt, Germany) and silicone dioxide (Aerosil 200) from Evonik-Degussa GmbH (Essen, Germany).

Table 1
The composition of the inner core containing 4.8 mg rivastigmine tartrate.

Components	mg	%	Function
Rivastigmine granulate < 420 mic	34.3	49.0	
MCC	28.6	40.8	Filler/Hardness enhancer
PVP K90	0.9	1.3	Binder
Rivastigmine tartrate	4.8	6.9	The active material
CaP granulate < 420 mic	27.3	39.0	
CaP	24.8	35.5	Water absorbing agent
EC7	1.0	1.4	Binder
CPVP	1.5	2.1	Intra disintegrant
CPVP	7.0	10.0	Inter disintegrant
Aerosil 200	0.7	1.0	Glidant
Mg stearate	0.7	1.0	Lubricant
Total	70	100	

2.2. Methods

2.2.1. Preparation of the inner tablet

The formulation of the inner tablet is presented in Table 1. A wet granulation method was used to prepare the blend for the compression in the tablet press. CaP powder was granulated in order to improve its flowability and compressibility. The granulated CaP also swells more efficiently than the CaP powder, allowing the lowering of the concentration of CaP in the formulation. For this purpose, the solution of a low viscosity ethylcellulose (EC7) (1.6 g) in ethanol (10 ml) was slowly added onto a mixture of CaP powder (40 g) and CPVP (2.4 g) while mixing with a mortar and pestle. The resulting mixture was then dried at 40 °C for about 16 h, which eventually yielded a water content of 3% as measured by a loss on drying method. Thereafter, the dried CaP granulate was milled and sieved through a 420 μ sieve using a Haver EML 200 digital T sieve shaker (HAVER & BOECKER, Oelde, Germany).

The granulation of rivastigmine tartrate was performed using a solution of rivastigmine tartrate (8.5 g which was carefully weighed directly into a beaker) and PVP K90 (1.6 g) in purified water (20 g). The solution was then slowly added onto MCC (50 g) while mixing with a mortar and pestle. The residues of the solution left in the beaker were rinsed with additional volume of purified water (5 ml) and also added onto the granules. The wet granules were then dried at 85 °C for 12 h which yielded a water content of 2.1%. The dried granules were finally milled and sieved through a 420 μ sieve.

Next, the rivastigmine tartrate granules were mixed with silicone dioxide (Aerosil® 200) (1.4 g) for 5 min to improve its flowability. The mixture was then transferred to a polyethylene bag and mixed with CPVP (14 g) and granulated CaP (54.6 g) for 20–30 min. Magnesium stearate (1.4 g) was added and mixed for an additional 2–3 min.

Biconvex 5 mm cores were compressed automatically using a Korsch EK-0 (Korsch AG, Berlin, Germany) single punch tablet press operated by an Erweka drive unit (AR 400) (ERWEKA GmbH, Heusenstamm, Germany). The cores weighed, on average, 70 mg (of 10 cores, with an RSD, relative standard deviation, of 0.5%) and presented a mean hardness of 10 Kp (RSD = 2.8%).

2.2.2. Coating process of the inner tablet

The coating process was performed using a unique combination formulation of ethylcellulose and CaP as detailed elsewhere [21].