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Design and evaluation of a specific, bi-phase extended release system based on differently coated mini-tablets

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ABSTRACT

Mini-tablets are gaining great attention as systems capable of being formulated into multiple unit systems providing a specific drug release pattern. Within the presented research a combined, multiple-unit system, based on different coated matrix mini-tablets, has been developed in order to achieve 24-h specific sigmoid extended release of the model drug paliperidone. The mini-tablets were based on different amounts of polyvinyl acetate/polyvinyl pyrolidone mixture as the matrix former, providing extended release, and two different types of pH-dependent, acrylic polymer coatings, providing delay in release onset, and thus achieving the required specific sigmoid release pattern imposed by the original drug on the market. The selected formulation proved to be consistent with pharmacopoeial requirements. It was also *in vitro* similar (f_2) to the original drug and the theoretical linear release profile, as well as robust and reproducible regarding *in vitro* release in different fasted gastro-intestinal conditions. This is proof of concept that 24-h, specific, and almost linear release profile of drugs with high solubility can be achieved by employing technology of coated matrix mini-tablets.

1. Introduction

The oral route of drug administration is still the most convenient one for patient's treatment, with solid oral dosage forms (tablets and capsules) being most often prescribed by physicians and/or advised by community pharmacists (Aulton, 2007). However, conventional tablets and capsules are not suitable for some specific and vulnerable population groups, such as paediatrics, geriatrics, or patients with impaired swallowing. These issues directed pharmaceutical scientists to develop more specific, personalised, and patient friendly solid oral dosage forms which will provide adequate treatment, and will overcome problems such as high dosing frequency, dosing inflexibility, impaired swallowing and polypharmacotherapy (EMA, 2011).

Mini-tablets (diameter $\leqslant 3$ mm) are emerging as a contemporary and promising type of solid oral dosage form for targeted patient groups. Mini-tablets are produced on standard tablet presses equipped with multiple tooling, wherein strict control of tablet tooling alignment, powder flowability, and maximal particle size are necessary in terms of obtaining suitable product and avoiding tooling damage (Aleksovski et al., 2015; Kachrimanis et al., 2005; Lennartz and Mielck, 1998; Mielck and Flamming, 1995). When formulated as multiple-unit systems (filled into capsules, sachets, or dispensers) mini-tablets may provide flexible dosing (Bredenberg et al., 2003) and alternatively also a combination of different drug release kinetics in one system, which subsequently could decrease the dosing frequency, improve therapeutic outcome, and decrease side effects (Goole et al., 2008; Krenzlin et al., 2011; Li and Zhu, 2004; Lopes et al., 2006; Mohamed et al., 2013). When taken directly in the mouth or mixed with soft food/drink, mini-tablets offer improved unit swallowing and a decreased incidence of aspiration and choking, compared to standard tablets and even to glucose syrup (Klingmann et al., 2013; Spomer et al., 2012; Tomson et al., 2009). Similar to other multiple-unit systems, mini-tablets give several biopharmaceutical advantages over single unit tablets and enteric-coated capsules such as broad gastro-intestinal distribution, leading to improved bioavailability and decreased side effects connected to increased local drug concentration; and less significant all-or-nothing effect (Abdul et al., 2010). Compared to pellets, microspheres, and coated granules, mini-tablets have more uniform size, shape, and porosity, which can assure a final product with better uniformity (weight and content) and also more reproducible and robust coating process (Munday, 1994). As a result, mini-tablets are ideal for development of robust multiple-unit modified release systems.

Paliperidone (9-hydroxy-risperidone) belongs to the class of atypical antipsychotics and is a major metabolite of the already well-established risperidone. As a second generation antipsychotic,

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paliperidone is effective in treating both positive and negative symptoms of schizophrenia with an increased safety effect towards extrapyramidal symptoms. According to its structure, paliperidone acts as a weak base whose solubility drops down with pH increase. Paliperidone is present on the market as a 24-h extended-release tablet, which is produced in the form of a three layer osmotic pump (OROS® push–pull). Formulated in this manner the tablet provides a specific sigmoidal release profile with less than 10% drug release in the first four hours, and up to 100% linear drug release in 24 h, providing the optimal ratio between the therapeutic benefit and side effect occurrence (EMA, 2007). Oral osmotic pump systems have many advantages, such as: pH-independent drug delivery, usually by zero order kinetics, longer-lasting extended release, and thus reduced dosing frequency, and an improved *in vitro–in vivo* correlation. Oral osmotic pump systems, however, also have several disadvantages such as: impaired swallowing due to large unit size, gastric transit affected by food, and relatively complicated and expensive production process (Ghosh and Ghosh, 2011; Gupta et al., 2010).

The aim of this research article was to develop a novel, patient-friendly, and cost-beneficial, 24-h extended-release, multiple-unit oral dosage form of the model drug paliperidone, based on different matrix mini-tablets coated with different pH-dependent polymers. This can, in our opinion, serve as proof of concept that 24-h, specific, sigmoidal and linear-like extended release profiles could be achieved also by employing technology of combined coated mini-tablets, i.e. at least for drugs that are not limited by sink conditions. Two types of matrix extended release mini-tablets (slower release and moderately faster release), based on polyvinyl acetate/polyvinyl pyrolidone mixture as a matrix former, were formulated and produced via a direct tableting process on a laboratory scale. Both types of mini-tablet formulations were then coated via a fluid-bed process and combined into a multiple unit dosage form in terms of obtaining the specific sigmoidal release profile, similar to the one of the commercial osmotic pump.

2. Materials and methods

2.1. Materials and formulation compositions

Paliperidone was purchased from MSN Laboratoires, India; Kollidon® SR (polyvinyl acetate/polyvinyl pyrolidone physical mixture in weight ratio 80:19) was kindly supplied by BASF, Germany; lactose monohydrate spray-dried was kindly supplied by DFE Pharma, Germany; dibasic calcium phosphate anhydrous (DI-CAFOS A150) was obtained from Chemische Fabrik Budenheim KG, Germany; magnesium hydroxide was purchased from Fluka, Switzerland; magnesium stearate was supplied from Faci S.P.A., Italy; Hypromelose 2910, 6 cps (HPMC 606) was purchased from the Harke Group, Germany; Polyethylene glycol 6000 (PEG 6000) was obtained from Fluka, Switzerland; Eudragit® L30 D-55 (L30 D55) and Eudragit® FS 30D (FS 30D) were a kind gift from Evonik, Germany; Triethyl citrate and Polysorbate 80 (Tween 80) were purchased from Sigma Aldrich, USA; and Glycerol monostearate was obtained from Lex, Slovenia. All other reagents were of analytical grade. The composition of single mini-tablet formulations and their examined combinations are given in Tables 1 and 2, respectively.

The most suitable formulations were chosen for further processing and coating in a laboratory fluid-bed coating apparatus. Coating compositions for achieving delayed release and colon targeted release are shown in Table 3.

2.2. Methods

2.2.1. Paliperidone saturated solubility

An excess amount of paliperidone was placed in contact with 50 ml 0.1 N HCl and phosphate buffers with pH 4.5; 5.5; 6.8; 7.4, respectively (prepared according to European Pharmacopeia – Ph.Eur. 8th edition), in terms of determining its solubility in these media. The samples were placed for half an hour into an ultrasonic bath, then for 24 and 48 h on a magnetic stirrer at 37 °C, and an additional half of hour in an ultrasonic bath. The supernatant was filtered through a 0.45 μm membrane filter; and assayed by HPLC method after 24 h and at 48 h. All experiments were conducted in triplicate.

2.2.2. Assessing paliperidone concentration by HPLC

Concentration of paliperidone during analysis of solubility, drug content and dissolution was assessed by HPLC method (Agilent 1100 Series, USA) adapted from Nageswara Rao et al., 2013. The mobile phase (and also diluent) consisted of an ammonium acetate buffer (pH = 4) and acetonitrile in a ratio of 70:30. Separation was performed by column Symmetry C18 (5 μm, 4.6 × 150 mm,

Table 2
Selected and evaluated mini tablet combinations.

Combinations	Composition[a]
C1	2 MT F2 + *2MT F1*
C2	1 MT F3 + *3 MT F1*
C3	1 MT F3 + *3 MT F2*
C4	1 MT F3 + *2 MT F2* + *1 MT F1*
C5	1 MT F3 + *2 MT F1* + *1 MT F2*
C6	1 MT F3 + *3 MT F12*

[a] Mini-tablets formulations in italic were only added after passage into media with pH of 7.4.

Table 3
HPMC-based barrier, duodenal, and colon delivery coating compositions per mini-tablet in mg.

Compound	Delayed release system	Colon-targeted system
HPMC 606	0.372	0.372
PEG 6000	0.046	0.046
Eudragit L30 D55	0.761	/
Eudragit FS30 D	/	1.387
Triethyl citrate	0.076	0.069
Glycerol monostearate	0.038	0.056
Polysorbate 80	0.015	0.022
Sum	1.308	1.952

Table 1
Mass percentage composition of studied single mini-tablet formulations.

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Paliperidone	10	10	10	10	10	10	10	10	10	10	10	10
Kollidon SR	20	30	40	20	30	40	60	20	30	30	30	30
Lactose monohydrate	69	59	49	/	/	/	/	35	30	49	44	54
Dibasic Ca phosphate	/	/	/	69	59	49	29	34	29	/	/	/
Mg hydroxide	/	/	/	/	/	/	/	/	/	10	15	5
Mg stearate	1	1	1	1	1	1	1	1	1	1	1	1