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Mini-tablets versus pellets as promising multiparticulate modified release delivery systems for highly soluble drugs

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ABSTRACT

Whether mini-tablets (tablets, diameters ≤6 mm) belong to single- or multiple-unit dosage forms is still questionable. Accordingly, Pharmacopoeial evaluation procedures for mini-tablets are lacking. In this study, the aforementioned points were discussed. Moreover, their potential for oral controlled delivery was assessed. The antidepressant venlafaxine hydrochloride (Vx), a highly soluble drug undergoing first pass effect, low bioavailability and short half-life was selected as a challenging payload. In an attempt to weigh up mini-tablets versus pellets as multiparticulate carriers, Vx-loaded mini-tablets were compared to formulated pellets of the same composition and the innovator *Effexor®XR* pellets.

Formulations were prepared using various polymer hydrogels in the core and ethyl cellulose film coating with increasing thickness. Mini-tablets (diameter 2 mm) showed extended Vx release (<60%, 8 h). Indeed, release profiles comparable to *Effexor®XR* pellets were obtained. Remarkably higher coating thickness was required for pellets to provide equivalent retardation. Ethyl cellulose in the core ensured faster release due to polymer migration to the surface and pore formation in the coat. mini-tablets showed higher stability to pellets upon storage. Industrially speaking, mini-tablets proved to be superior to pellets in terms of manufacturing, product quality and economical aspects. Results point out the urgent need for standardized evaluation procedures for mini-tablets.

1. Introduction

Oral multiparticulate drug delivery systems such as nano-/microparticles, granules, pellets and mini-tablets are dosage forms mainly consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substance is divided on a plurality of subunit, typically consisting of particles with diameter of 0.05–2 mm (Kulkarni et al., 2010; Srivastava and Mishra, 2010). To deliver the recommended total dose, these subunits are typically filled into a sachet, encapsulated or compressed into a tablet (Kulkarni et al., 2010). Recently, much emphasis is being laid on the development of multiparticulate dosage forms in preference to single unit, monolithic systems because of their potential benefits such as better distribution, facilitated disintegration, increased bioavailability, reduced risk of both systemic toxicity and local irritation (Asghar and Chandran, 2006).

Mini-tablets, also termed as mini-matrices in 1990s, were considered as multiparticulate system that combine the physiological advantages of multiple unit dosage forms and the economic advantages of single unit dosage forms (Sujja-areevath et al., 1996). Compared to other multiparticulate systems such as granules or pellets, mini-tablets reveal several advantages; compression of mini-matrices represents an attractive alternative to irregularly-shaped granules or pellets. The defined size, robust mechanical properties, constant specific surface area, smooth outer surface, small variability within and between batches contribute to more reproducible coating with less coating material than granules (Abdulhadi et al., 2012; Tissen et al., 2011). When related to single unit dosage forms, mini-tablets exhibit several benefits like minor risk of dose dumping and independence of the rhythm of food transport (Follonier and Doelker, 1992; Tissen et al., 2011).

Mini-tablets are prepared either by dry mixing or wet granulation and then compressed using conventional rotary compressing machine equipped with multi-tip punches. For application, the compacts can be filled into hard gelatin capsules or can be administered with a dose dispenser for individual dosing

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(Bredenberg et al., 2003; Tissen et al., 2011) or compacted into bigger tablets that, after disintegration, release these subunits as multiple dosage forms (Abdulhadi et al., 2012; Lopes et al., 2006). Accurate official specifications regarding the diameter of mini-tablets are lacking; from literature some authors defined mini-tablets with diameters up to 6 mm, previous studies referred to mini-tablets as mini-matrices with diameter 3, 4.5 and 5.5 mm (Sujja-areevath et al., 1996), whereas Munday and Fassihi (1995) developed novel controlled release theophylline capsule (Minitab) containing mini-matrices of 3 mm in diameter.

To date, mini-tablets were developed serving for various applications; with respect to poorly compressible drugs such as pancreatin, the reduction of tablet diameter from 10 mm to 2 mm enabled higher drug loads (Tissen et al., 2011). Cylindrical pancreatin micro-tablets with a diameter of 1–2.5 mm have been patented (Lennartz and Mielck, 1998; Tissen et al., 2011). Lennartz and Mielck (Lennartz and Mielck, 1998) supported this statement by comparing tablets of different sizes containing acetaminophen. To the best of our knowledge, the manufacturing of mini-tablets below 1.5 mm diameter has not been yet reported. Regarding modified drug delivery, matrix mini-tablets and biphasic delivery systems were developed and investigated (De Brabander et al., 2000; Tissen et al., 2011). These systems can produce a rapid rise in plasma concentrations that are requested to promptly exercise the therapeutic effect, followed by an extended release phase in order to avoid repeated administrations (Maggi et al., 1999). For instance, a biphasic delivery system for diclofenac sodium was prepared by compressing fast release granular components (dissolved within the first 15 min) as well as compressed mini-tablets (provided different release rates) (Patel and Patel, 2011).

Venlafaxine hydrochloride (Vx), a novel third generation antidepressant mainly acting by selectively inhibiting the uptake of serotonin and noradrenaline, was selected as a challenging model in the current study (Ibor et al., 2008). Due to high water solubility, first pass metabolism, low bioavailability and short half-life, extended release formulation of Vx became a prime requirement to eliminate multiple daily dosage and minimize side effects. Once daily matrix tablets of Vx (9 and 11 mm diameter) formulated with swellable and non-swellable polymers ensured Vx release over a period of 16 h (Makhija and Vavia, 2002). In another study, Vx was intercalated with montmorillonite then coated with polyvinylpyrrolidone (PVP). Composites provided extended release for 48 h (Hasmukh Patel et al., 2011). Meanwhile, montmorillonite-based Vx-PLGA nanocomposite were developed as oral controlled release delivery system (Jain and Datta, 2014). Peng et al. developed chitosan/glycerophosphate thermosensitive hydrogel for Vx (Peng et al., 2013). *In vitro* release profiles illustrated controlled drug delivery over 24 h, while *in vivo* pharmcokinetic studies in rabbits demonstrated higher plasma concentration of Vx after subcutaneous administration of hydrogel compared to Vx saline solution. On the other hand, mouth dissolving tablets of Vx were formulated using camphor as sublimating agent to increase porosity and indion 234 as super-disintegrant. The formulation was optimized through a factorial design (Pathan et al., 2013). In line with our interest in multiparticulate carrier systems, Vx coated pellets were recently reported to ensure sustained release at different pHs. The relative bioavailability studied in beagle dogs following oral administration revealed significant differences compared to the reference (Liu et al., 2012). Interestingly, Vx mini-tablets 6.3 mm diameter filled into hard gelatin capsule were developed. A sustained release was obtained using HPMC of various viscosity grades and Kollidone (Anusha et al., 2013).

This study aims, for the first time to our knowledge, at weighing up mini-tablets versus pellets as efficient multiparticulate modified release approaches for Vx. This involves comparative evaluation of different parameters such as diameter, thickness, hardness, friability, binder (polymer) concentration, weight gain by coating, content uniformity, bulk and tapped density, flowability and release pattern. The release profile of Vx from selected formulae of both pellets and mini-tablets are to be compared to the innovator product *Effexor® XR* pellets.

Table 1A
Composition of mini-tablets MT1/MT2 and pellets formulae FP1/FP2 (amount expressed in g%).

Core Composition (g%)	Formulation			
	Mini-tablets		Pellets	
	MT1	MT2	FP1	FP2
Venlafaxine hydrochloride	30	30	30	30
Lactose monohydrate	20	19	20	17
Avicel PH 101	15.5	10.5	11	9
Maize starch	30	28	30	25
Ethyl cellulose	–	10	–	10
Polyvinyl pyrrolidone K30 (PVP K30)	2	2	2	2
Polyethylene glycol 6000 (PEG 6000)	–	–	4	4
Gelatin	–	–	1	1
Talc powder	2	2	2	2
Magnesium stearate	0.5	0.5	–	–

2. Materials and methods

2.1. Materials

Venlafaxine HCl, Eudragit RS 100 and PVP were kindly gifted from AARTI Industries Limited, India, Evonik Röhm GmbH Pharma Polymers, Germany and BASF, Germany, respectively. Lactose monohydrate was purchased from Danone GmbH, Germany. Avicel PH101 was obtained from Mingtai Chemical Co. Ltd., India, talc powder from Golcha Associated Exports, India and Maize starch from National Company for Maize products, Egypt. Both acetone and triethyl citrate were purchased from Sigma–Aldrich, Germany, while ethyl cellulose (Ethocel® standard 100 premium) was from Colorcon, Germany. Both PEG 6000 and Magnesium stearate were obtained from Esteem Industries PVT. LTD, India, and Hangzhou Zongbao Imp. & Exp. Corp., Ltd., China, respectively. Gelatin was obtained from Ste Ciale TARDY & CIE, France.

2.2. Methods

2.2.1. Preparation of Vx-loaded mini-tablets and pellets

2.2.1.1. Core mini-tablets and pellets. Two formulations of mini-tablets (MT1 & MT2) as well as pellets (FP1 & FP2) containing 30% w/w Vx were prepared according to composition described in Table 1A.

Minitablets were prepared by geometrically mixing the drug with diluents (lactose monohydrate, microcrystalline cellulose and maize starch). The powder mix was kneaded with binder solution (PVP K30 aqueous solution, 15% w/v, for formula MT1) or (ethyl cellulose in acetone, for formula MT2) to form dense granules, then allowed to dry in oven at 70 °C to reach a moisture content of 1–2%.

Table 1B
Composition of ethyl cellulose coating dispersion.

Coat composition	Weight (g)
Ethyl cellulose®/ Eudragit®RSPO	30
Triethyl citrate (TEC)	6
Quinoline yellow lake	0.01
Talc powder	20
Acetone	944
Total	1000