Saudi Pharmaceutical Journal (2016) **24**, 57–63

King Saud University

Saudi Pharmaceutical Journal

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ORIGINAL ARTICLE

Enhanced *ex vivo* intestinal absorption of olmesartan medoxomil nanosuspension: Preparation by combinative technology

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Received 20 February 2015; accepted 13 March 2015
Available online 20 March 2015

KEYWORDS

Nanosuspension;
Combination methods;
Particle size;
Intestinal absorption

Abstract The purpose of this study was to develop nanosuspension based on combinative technology to enhance the intestinal absorption of Olmesartan medoxomil (OLM), a potent antihypertensive agent with limited oral bioavailability. Two combinative approaches were employed and then characterized. *In vitro* intestinal absorption of OLM nanosuspension and plain OLM was studied using non-everted rat intestinal sac model. Optimal OLM nanosuspension was prepared by a combination of ball milling and probe sonication using stabilizer, Poloxamer 407. The formula exhibited particle size of 469.9 nm and zeta potential of −19.1 mV, which was subjected to *ex vivo* studies. The flux and apparent permeability coefficient in intestine from OLM nanosuspension was higher than the plain drug, thereby suggesting better drug delivery.

Abbreviations: OLM, olmesartan medoxomil; P407, Poloxamer 407; HPH, high pressure homogenization; PDI, polydispersity index

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

1. Introduction

Drug solubility is a crucial factor limiting the therapeutic advantage of many potent drugs because of low oral bioavailability. The conventional approach to enhance oral bioavailability of drugs with very low aqueous solubility includes use of co-solvents, salt formation, pH adjustment, emulsions and micellar dispersions, micronization and complexation with cyclodextrins (Lawrence and Rees, 2000; Nakano, 2000; Stella and Rajewski, 1997). These approaches are useful, but possess some limitations such as the use of large amount of excipients and sophisticated equipment. An alternative method is nanonization of drug and stabilization using stabilizers, termed as nanosuspension (particle size in nanometer range). Nanosuspensions are reported to increase saturation solubility due to reduced particle

http://dx.doi.org/10.1016/j.jsps.2015.03.008
1319-0164

size and increased surface area, contributing to enhanced dissolution and eventually increased bioavailability (Kesisoglou et al., 2007; Kocbek et al., 2006; Liversidge and Cundy, 1995). Broadly, there are two methods for preparation of nanosuspension, bottom-up (precipitation) and top-down (Rabinow, 2004; Merisko-Liversidge et al., 2003). The top down technologies are based on particle fragmentation to submicron units and include ball milling and high-pressure homogenization (Keck and Muller, 2006; Jacob et al., 2000). Top-down method is widely accepted to reduce particle size of drug and proved to be successful; however, combinative technologies are recently used to produce even smaller particles or reduce the processing time to prepare nanosuspension. Combinations of ball milling, lyophilization or precipitation with high pressure homogenization (HPH) are the reported methods under combinative technologies (Salazar et al., 2012a, 2013b).

Olmesartan medoxomil (OLM) is a selective AT1-subtype angiotensin-II receptor antagonist used for the treatment of hypertension (Warne and Jarvis, 2002). The aqueous solubility of OLM is < 7.75 μg/ml and oral bioavailability of the tablet is only 26% in healthy humans (Prajapati et al., 2013). The unabsorbed drug leads to gastrointestinal side effects such as abdominal pain, dyspepsia, gastroenteritis and nausea. The nanosuspension of OLM was reported to enhance its bioavailability (Thakkar et al., 2011). In the present study, an effort was made to prepare nanosuspension of OLM by a combination of top down methods and evaluate the effectiveness of combinative methods in enhancing the intestinal absorption of OLM.

2. Methods

2.1. Preparation of nanosuspension

The nanosuspensions of OLM were prepared by combinative technologies. Two methods were employed in the present study viz. ball milling followed by probe sonication and high speed homogenization followed by probe sonication. Various concentrations of stabilizers such as PVA and Poloxamer 407 (P407) were used to stabilize the nanosuspensions (Table 1). Briefly, 30 mg of OLM was dispersed in 15 ml of stabilizer solution and homogenized (Polytron PT 1300D, Singapore) or ball milled (PM100, Retsch, Germany) followed by probe

Table 1 Preparation of nanosuspensions of OLM.

S. no.	Code	Stabilizer	Concentration (%)	Time of probe sonication (min)
1	BM1	Poloxamer 407	0.5	15
2	BM2	Poloxamer 407	0.5	10
3	BM3	Poloxamer 407	0.25	15
4	BM4	Poloxamer 407	0.25	10
5	BM5	Poloxamer 407	0.125	15
6	BM6	Poloxamer 407	0.125	10
7	BM7	Poloxamer 407	0.1	15
8	BM8	Poloxamer 407	0.1	10
9	BM9	PVA	0.5	30
10	BM10	PVA	0.25	30
11	BM11	PVA	0.25	15
12	HSH1	Poloxamer 407	0.125	15
13	HSH2	PVA	0.25	15

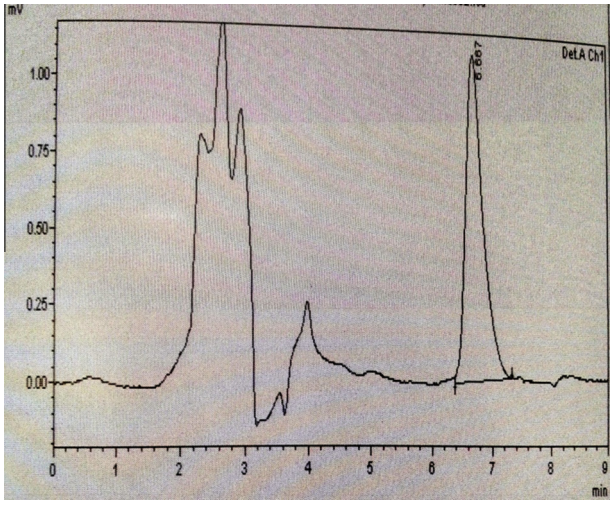

Figure 1 HPLC chromatogram of olmesartan medoxomil.

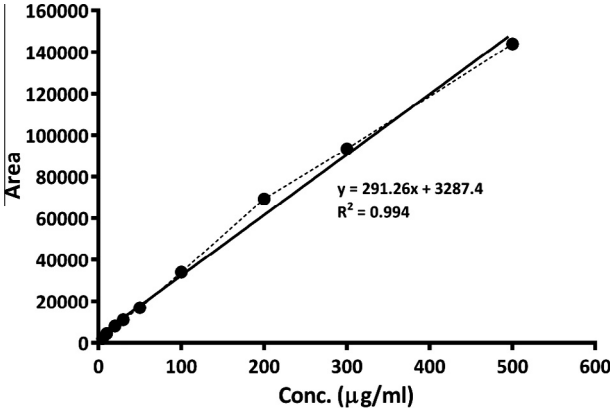

Figure 2 Calibration curve of OLM using HPLC–UV method.

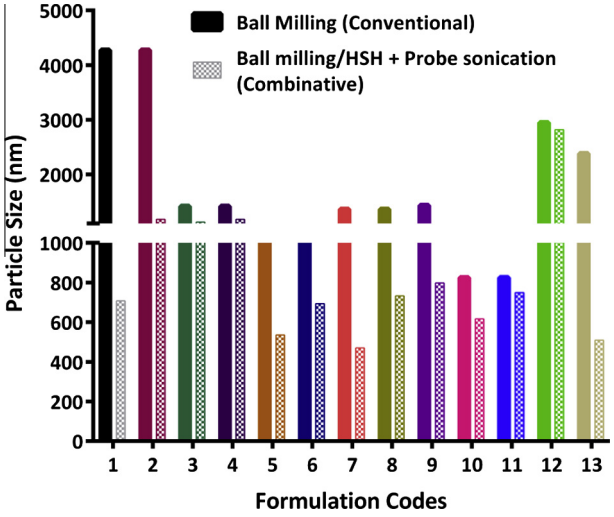

Figure 3 Particle size of nanosuspensions after conventional and combinative technologies.