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ORIGINAL RESEARCH

# Venlafaxine-loaded sustained-release poly(hydroxyethyl methacrylate-*co*-itaconic acid) hydrogel composites: their synthesis and in vitro/in vivo attributes

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**Abstract**
Hydrogels have potential applications as sustained-release drug delivery systems, as an example in treatment of major depressive disorders. This paper reports some works carried out to obtain a new type of copolymeric hydrogel for an anti-depressant drug. The copolymerization of itaconic acid, hydroxyethyl methacrylate (HEMA), and tetraethyleneglycol dimethacrylate was performed. The gels were evaluated for swelling, diffusion coefficient, drug incorporation, in vitro dissolution, and in vivo performance in rabbits after oral administration. The pharmacokinetic parameters like bioavailability, $C_{max}$ and $T_{max}$ were calculated for hydrogels in comparison to oral solution containing equivalent amount of venlafaxine. The HEMA-based matrices showed negligible swelling and release rate of venlafaxine, which were also very low in a buffer of pH 1.2. However, both the swelling and release rate of venlafaxine were faster at high pH (6.5 and 7.5). The $T_{max}$ of the formulation with the highest swelling and release rate ($T_1$) were found at 600 min compared to that at 180 min for oral solution having equivalent quantity of venlafaxine. $AUC_{0-\infty}$ for oral hydrogel was 2.1 times greater than that for oral solution of venlafaxine. Similarly, MRT for hydrogel was 3.1 times more than that for oral solution. However, $C_{max}$ for oral cross-linked hydrogel composite was significantly lower than that for equivalent amount of oral drug solution. The synthesized hydrogel composites showed a promising ability for sustained release of venlafaxine both in vitro and in vivo. It was found that venlafaxine delivery through oral route was practical.

**Keywords** Poly(hydroxyethylmethacrylate-*co*-itaconic acid) hydrogel · Sustained-release venlafaxine · Copolymerization · Physicochemical testing · Pharmacokinetic parameters

## Introduction

Venlafaxine is a novel third-generation anti-depressant drug, chemically a bicyclic phenylethylamine derivative that differs structurally from currently available anti-depressant drugs [1, 2]. The drug is devoid of many side effects related to tricyclic anti-depressants and selective serotonin reuptake inhibitors [3]. It is superior to selective serotonin reuptake inhibitors in preventing treatment resistant recurrence of depression. The drug has shown efficacy as analgesic in neuropathic pain and reduces anxiety associated with premenstrual disphoric disorders. Venlafaxine hydrochloride is a white crystalline solid having water solubility (572 mg/mL). It can be administered at 75–450 mg/day doses. Due to short half-life, it is administered 2–3 times a day. Therefore, frequent administration of drug necessitates development of sustained-release formulations [4, 5].

The uses of hydrogels in drug delivery, tissue engineering, cell encapsulation, ophthalmic, and vascular prostheses has shown good biocompatibility [6, 7]. The unique characteristic of volume changes of smart hydrogels in response to temperature, pressure, pH, and biological target (receptor, antibody, growth factor, etc.) has made them highly valuable

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