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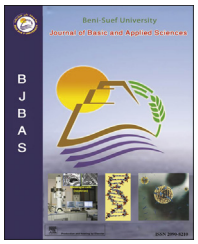

Full Length Article

Development and evaluation of gastroretentive floating tablets of an antidepressant drug by thermoplastic granulation technique

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ABSTRACT

The present study was undertaken with an aim to formulate, develop and evaluate gastroretentive floating tablets of an antidepressant drug, Venlafaxine HCl (hydrochloride), which release the drug in a sustained manner over a period of 24 h. Three different hydrophobic retardants namely hydrogenated cottonseed oil, carnauba wax, cetyl alcohol and a hydrophilic polymer Methocel® (hydroxy propyl methyl cellulose (HPMC)) K15M were used in different combinations at different ratios for the preparation of tablets. The tablets were prepared by Hot Melt or Thermoplastic granulation method and evaluated for tablet thickness, hardness, weight variation, friability, floating lag time and in vitro drug release. Formulation F8 with hydrophilic polymer (Methocel® K15M) and hydrophobic retardant (carnauba wax) in the ratio 1:2.6 (approx.) was considered as an optimized formulation. The optimized formulation showed satisfactory sustained drug release and remained buoyant on the surface of the medium for more than 24 h and its release profile was comparable with the marketed formulation (VENTAB-XL 37.5). It can also be concluded that floating drug delivery system of Venlafaxine HCl can be successfully formulated as an approach to increase gastric residence time and thereby improving its bioavailability.

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1. Introduction

Oral sustained drug delivery system is complicated by limited gastric residence time. Rapid gastrointestinal transit can prevent complete drug release in the absorption zone and reduce the efficacy of administered dose, since the majority of drugs are absorbed in stomach or the upper part of small intestine (Choi et al., 2008; Mahant and Nasa, 2011). Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability (Kaza et al., 2009). Venlafaxine HCl is a unique antidepressant, and is referred to as a serotonin, norepinephrine-dopamine reuptake inhibitor (Keith, 2006). Venlafaxine HCl is a highly water soluble drug (Nidadavolu, 2014). Venlafaxine HCl and its active metabolite, o-desmethyl venlafaxine (ODV) inhibit the neuronal uptake of norepinephrine, serotonin and to a lesser extent dopamine (Ric et al., 1991). Hence it lacks the adverse anticholinergic, sedative and cardiovascular effects of tricyclic antidepressants (Simona and Aguiar, 2004) .The steady state half-lives of Venlafaxine HCl and ODV are 5 and 11 h, respectively, necessitating the administration 2 or 3 times daily so as to maintain adequate plasma levels of drug (Troy et al., 1995). The half-life of Venlafaxine HCl is relatively short, and, therefore, patients are directed to adhere to strict medication routine, avoiding missing a dose. Even a single missed dose can result in the withdrawal symptoms (Parker and Blennerhassett, 1998). In such case the formulation releasing the drug in sustained manner will aid the patient to adhere to strict medication routine by avoiding the need to take the dosage form 2 or 3 times daily. The use of sustained release formulation is associated with less nausea and dizziness (Olver et al., 2004).

The objective of the present research work was to provide gastroretentive formulation that will provide once-daily, sustained release dosage form. The swellable hydrophilic polymer Methocel® K15M (hydroxy propyl methyl cellulose) and hydrophobic retardants like hydrogenated cottonseed oil, carnauba wax and cetyl alcohol were tried at different ratios to prepare various formulations of Venlafaxine HCl.

2. Materials and methods

Venlafaxine hydrochloride was obtained as a gift sample from Amoli Organics Pvt. Ltd., Vadodara, India. Carnauba Wax, cetyl alcohol and Talc were procured from SD Fine Chemicals, Mumbai. Hydrogenated cottonseed oil was obtained as gift sample from Zhaveri Pvt. Ltd., Mumbai. Methocel® K15M (hydroxy propyl methyl cellulose) was obtained as gift sample from Colorcon Asia Pvt., Ltd. Goa, India. All other excipients and chemicals used were of analytical grade. VENTAB-XL 37.5 (Batch no. DN3651) was procured from the local market.

2.1. Drug–excipients interaction study and identification

2.1.1. Fourier transform infrared spectroscopy (FTIR)

An infrared spectrum of pure drug, mixture of drug with each retardant and physical mixture of optimized formulation was recorded using SHIMADZU FTIR Spectrophotometer. The scanning range was 500–4000 cm^{-1} and the IR spectra of samples were obtained using KBr disc method. Any change in spectrum pattern of drug due to presence of polymers was investigated to identify any chemical interaction.

2.1.2. Differential scanning calorimetry (DSC)

The possibility of drug–excipient interaction was further investigated by differential scanning calorimetry. DSC analysis was performed using SIECKO SII EXSTAR DSC 6220 Software on 10 mg sample. Samples were heated in aluminum pan at a rate of 10 °C/min. within a 30–305 °C temperature range under a nitrogen flow of 10 ml/min. Alumina was used as a reference.

2.1.3. UV spectroscopy (determination of λ (lambda)$_{max}$)

The stock solution (1000 μg/ml) of Venlafaxine HCl was prepared in distilled water. This solution was appropriately diluted with distilled water to obtain a concentration of 3 μg/ml. The UV spectrum was recorded in the range of 200–400 nm on Shimadzu double beam UV–visible spectrophotometer. The same procedure was carried out in 0.1 N HCl (hydrochloric acid, pH 1.2). The spectrum and wavelength of maximum absorption were recorded.

2.2. Preparation of standard curve

The stock solution (1000 μg/ml) of Venlafaxine HCl was prepared in 0.1 N HCl. From this 30 μg/ml second stock solution was made. This was withdrawn as 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 ml and diluted each with 0.1 N HCl (pH 1.2) to obtain concentrations of 3, 6, 9, 12, 15, 18, 21, 24, 27 and 30 μg/ml. The absorbance of these solutions were measured at 225 nm against blank i.e. 0.1 N HCl. Same procedure was followed for the preparation of standard curve of distilled water. The coefficient of correlation and equation for the line are determined.

2.3. Preparation of Venlafaxine HCl effervescent tablet

Effervescent floating tablets, each containing 37.5 mg Venlafaxine HCl were prepared by melt granulation method. The composition of various formulations is shown in Table 1.All the ingredients except wax were passed through sieve 40. The wax/oil were melted in porcelain dish on hot plate and drug was added to it. Then to this mixture other sieved ingredients except talc were added. The resultant mixture was allowed to solidify at room temperature and then passed through sieve 16 to form granules. The granules were lubricated by adding talc extra granularly. The lubricated granules were then compressed into a tablet using 10 mm standard flat-face punches on single punch tableting machine (Royal Artist Pvt.