CHAPTER 1
AIM OF PRESENT WORK
Venlafaxine hydrochloride is a novel antidepressant. Venlafaxine is well absorbed when given by oral route. It is extensively metabolized in liver. The major active metabolite is O-desmethyl venlafaxine. The short biological half-life (5 ± 2 hrs) and the fast clearance make the drug a suitable candidate for the development of once a day formulation. Furthermore, it is an antidepressant and so it is required to be taken for quite a long period. The recommended dose of venlafaxine HCl is 75 mg to 450 mg/day. The drug needs to be formulated in sustained release dosage form to improve the patient compliance as well as to reduce side effects like nausea and vomiting (Olyer et al., 2004).

In the recent years, preparation of matrix tablet has been demonstrated with the publication of numerous patents and research papers and their utilization in new products. The widespread and successful use of such polymeric systems could be attributed to their ease of manufacturing, relatively low cost, high biocompatibility, favorable in vivo performance and versatility in controlling the drug release with a wide range of physicochemical properties (Durig & Fassihi, 2002).

Various synthetic, semi synthetic and natural polymers are available for controlling the release of active pharmaceutical ingredients. Natural polymers have some disadvantages like batch to batch variability in source as well as microbial contamination. Hydrophilic polymers have been given considerable attention in the formulation of controlled release drug delivery systems for various drugs. Hypromellose, Hyprollose, sodiumcarboxymethylcellose, Carbopols®, xanthan gum, polyethylene oxide, guar gum and polyvinyl alcohol are a few representative examples of the hydrophilic polymers that have been extensively used in the formulation of controlled release system.

Hypromellose, formerly known as hydroxypropyl methylcellulose (HPMC) is widely used in the preparation of oral controlled drug delivery systems. Its non-toxic nature and ease of handling makes it an excellent release retardant material. On exposure to aqueous fluids, the polymer present in tablet hydrates to form a viscous gel layer through which the drug is released by diffusion and/or erosion of the matrix (Gohel et al., 2007). It is

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1. Aim of Present Work

available in various grades. Hypromellose is fast hydrating polymer and hence it is suitable for modifying the release of highly soluble drugs. The advantages of hypromellose are good solubility in water as well as in organic solvent, nonionic nature, thermal gelation, metabolic inertness, resistance to enzymes, compatibility, low taste and odor and stable to wide pH range (2.0 to 13.0). Hence, it was selected for controlling the release of venlafaxine HCl.

Polyethylene oxides (Polyox) are also extensively used in pharmaceutical industry. They are also available in various viscosity grades hence can be used as per the requirements of the formulation. They are suitable for direct compression, wet granulation or melt granulation technique. Polyox WSR 303, a high viscosity grade polyethylene oxide, will be used to develop venlafaxine HCl coated and layered tablets.

Xanthan gum, a natural carbohydrate, is commercially produced by fermenting glucose with the appropriate micro-organisms. It is the only bacterial polysaccharide produced industrially on a large scale. Xanthan gum swells in gastric fluid to produce a highly viscous layer around the tablet through which the drug can diffuse. This property makes xanthan gum a useful ingredient for controlled and sustained release applications. Xanthan gum will be evaluated as a hydrophilic matrixing agent for development of layered tablets of venlafaxine HCl.

Developing an ER formulation of freely soluble venlafaxine HCl (572 mg/mL) is a challenging task. Hydrophilic matrix tablets are attractive ER dosage forms, however highly water soluble drugs formulated with hydrophilic matrices may show an initial burst effect. The commercial ER formulation of venlafaxine HCl, Effexor XR is an extended release capsule containing coated pellets. The drug release from coated pellets is controlled by diffusion through the coating membrane. US patents 6,607,751 and 7,090,867 reported the use of cellulose ether (hypromellose) along with microbial polysaccharides for development of modified release tablet of venlafaxine HCl (Odidi, I., & Odidi, A. 2003, Odidi, I., & Odidi, A. 2006). US patents 6274171 and 6403120
1. Aim of Present Work

employed coating of spheroids with water insoluble excipients like ethyl cellulose (Sherman, Clark, Lamer & White, 2001, Sherman, Clark, Lamer & White, 2002).

The objective of the present study was to formulate an extended released hydrophilic matrix formulation of venlafaxine HCl by by-passing the existing patents and to elucidate the release kinetics of venlafaxine HCl from these matrices. Two approaches will be investigated in the current study. The first approach will be involving the use of barrier membrane coating with pore formers onto a hydrophilic matrix tablet, while the other approach will consist of preparation of triple layered matrix tablets (Siahi et al., 2005, Conte and Meggi, 1998 and Maggi et al., 2000).

The dosage forms will be developing by adopting a systematic approach, i.e. by adopting the concept of design of experiments (DOE) so that the concepts of quality by design (QBD) can be put in practice. Characterization of dosage form will also been done. More stress will be given to dissolution studies in suitable media such as distilled water suggested by US FDA. Optimized formulation from both the categories (coated and layered tablets) will be additionally examined for drug content, drug release in media with different pH, drug release in presence of ethanol, water uptake and swelling study. We intended to use rotary tablet machine only for preparing dosage form so that the optimized formulations can be taken up for further scale up.
1. Aim of Present Work

References


