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Carbamazepine solubility enhancement in tandem with swellable polymer osmotic pump tablet: A promising approach for extended delivery of poorly water-soluble drugs

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ABSTRACT

Elementary osmotic pump (EOP) is a unique extended release (ER) drug delivery system based on the principle of osmosis. It has the ability to minimize the amount of the drug, accumulation and fluctuation in drug level during chronic uses. Carbamazepine (CBZ), a poorly water-soluble antiepileptic drug, has serious side effects on overdoses and chronic uses. The aim of the present study was to design a new EOP tablet of CBZ containing a solubility enhancers and swellable polymer to reduce its side effects and enhance the patient compliance. Firstly, a combination of solubilizing carriers was selected to improve the dissolution of the slightly soluble drug. Then, designing the new EOP tablet and investigating the effect of different variables of core and coat formulations on drug release behavior by single parameter optimization and by Taguchi orthogonal design with analysis of variance (ANOVA), respectively. The results showed that CBZ solubility was successfully enhanced by a minimum amount of combined polyvinyl pyrrolidone (PVP K30) and sodium lauryl sulfate (SLS). The plasticizer amount and molecular weight (MW) together with the osmotic agent amount directly affect the release rate whereas the swellable polymer amount and viscosity together with the semi-permeable membrane (SPM) thickness inversely influence the release rate. In addition, the tendency of following zero order kinetics was mainly affected by the coat components rather than those of the core. Further,

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orifice size does not have any significant effect on the release behavior within the range of 0.1 mm to 0.8 mm. In this study we report the successful formulation of CBZ-EOP tablets, which were similar to the marketed product Tegretol CR 200 and able to satisfy the USP criterion limits and to deliver about 80% of CBZ at a rate of approximately zero order for up to 12 h.

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1. Introduction

Oral delivery remains as the most preferable and convenient route of administration for majority of drugs. Although they provide a suitable balance of efficacy and safety with acceptable clinical performance [1], conventional immediate release (IR) dosage forms have severe adverse action due to dose fluctuation and more importantly, low patient compliance caused by frequent doses [2,3]. Therefore, the rationale for development of an ER formulation of a drug is to improve the patient compliance with prescribed dosing regimens, enhance the therapeutic effects, minimize the dose and hence the side effects [1].

The osmotic pump tablet (OPT) is distinguished by utilizing the osmotic pressure as energy source for drug release, and it represents one of the most promising technologies for ER delivery systems [4,5]. Thirty-one products have been developed and marketed based on osmotic technology and 161 patents were published on the formulation aspects of these systems until the year 2000. In addition to being potentially able to provide a constant release independently to the characteristics of the release medium [4], these devices possesses distinctive clinical benefits, such as minimizing the food-effect and the improvement of the treatment tolerability and patient compliance [6]. Various types of OPTs have been developed and studied to deliver drugs with different aqueous solubilities [7].

The convenience and simplicity to manufacture and evaluation, has contributed much to the popularity and commercialization of EOPs over other osmotic based systems [8]. They consist of a core, containing the active agent, an osmogent and other excipients, coated with SPM. One orifice is drilled in the SPM through which the drug is released after the generation of osmotic pressure by the osmogent when exposed to an aqueous environment [9]. EOPs are commonly used to deliver water-soluble drugs but recently, some researches had been carried out to enable the delivery of water-insoluble drugs by EOPs [10]. Various attempts were utilized, such as addition of a solubility modulating agent to the core formulations [11], crystal-habit modifying agents for drugs, like polymers, surfactants and/or wicking agents [12].

CBZ, a dibenzapine derivative, is widely used for the treatment of epilepsy to control different types of seizures. The drug absorption from IR dosage forms was slow and erratic [13] and at overdoses and chronic use, CBZ exerts serious side effects which signify the importance of its incorporation into ER system. It also presents a poor aqueous solubility which results into poor bioavailability after oral administration [14]. Many previously published researches have reported a successful improvement of CBZ solubility using solid dispersion technique [13,15–17]. However, the use of large amounts of polymer constitutes one of the major drawbacks due to difficulties in handling and formulation into a final dosage form especially for such high drug loading. Further, in solid dispersion, maintaining the physical stability of the drug and the vehicle still one of the major problems together with the preparation technique and the difficulty in up scaling [18].

Therefore, CBZ incorporation into an effective EOP delivery system along with its solubility enhancement would improve the bioavailability, reduce the side effects and avoid fluctuation in plasma level [19].

In the present study, the development of a new design EOP tablet for the poorly water-soluble drug (CBZ) by solubility enhancement and incorporation of swellable polymer into the core tablet, have been investigated and aimed to achieve an optimum USP limit, zero order release, once daily administration. Minimum amounts of a hydrophilic polymer (PVP K30) and surfactant (SLS) were combined by simple physical mixing and used as solubility promoter in order to prevent the agglomeration of drug particles and increase their wettability. Swellable polymer Hydroxypropyl methylcellulose (HPMC) that was used in core formulations helps in formation of uniform gel containing drug particles to be pushed out of the device after water imbibitions and acts as another driving force for drug release apart from osmotic pressure. The core and SPM components were optimized using single parameter analysis and Taguchi orthogonal array design (OAD), respectively, including the type and amount of osmotic agent, swellable polymer and plasticizer, SPM thickness and orifice size. The effect of these factors on the release rate and kinetics was discussed and the developed systems were statistically compared with marketed ER CBZ tablets.

2. Materials and methods

2.1. Materials

CBZ powder was purchased from Zhejiang Jiuzhou Pharmaceutical Co. Ltd. (Zhejiang, China). Cellulose acetate (CA, opadry CA 500F 190001) and HPMC (E5, K100LV and K100M) were from Shanghai Colorcon Coating Technology Ltd. (Shanghai, China). PVP K30 was from ISP. (Shanghai, China).

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