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Rational design and *in-vivo* estimation of Ivabradine Hydrochloride loaded nanoparticles for management of stable angina

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ABSTRACT

Stable angina or angina pectoris is referred to as uneasiness/pain in the chest, resulting from coronary heart disease (CHD). Ivabradine Hydrochloride (IBH) is a recently approved drug to manage stable angina and heart failure symptoms. The approved IBH tablets exhibit some technical shortcomings i.e. short half-life (2 h), variable systemic absorption, and high first-pass metabolism (> 50%). Therefore, utilizing a nanoformulation technique, we have designed a differentiated and innovative formulation of IBH. The IBH loaded polymeric nanoparticles (IBH-PNPs) are being developed for per-oral delivery by double emulsion method, using Poly lactic-*co*-glycolic acid (PLGA) as polymer, and D-α-tocopherol polyethylene glycol 1000 succinate (TPGS) as a stabilizer. The pre-formulation studies performed are UV spectroscopy, FT-IR, and X-ray diffraction. The Box-Behnken design was exploited for formulation optimization. The optimized formulation was characterized for its particle size, zeta potential, morphology, entrapment efficiency, in-vitro release, stability studies, ex-vivo permeability, and in-vivo pharmacodynamics study. The optimized IBH-PNPs were found to be spherical (< 200nm) and exhibited normal size distribution under transmission electron microscopy and atomic force microscopy respectively. The zeta potential and entrapment efficiency were found to be −43.75 mv and 60 ± 4.8% respectively. Developed IBH-PNPs analyzed for *in-vitro* drug release where they exhibited biphasic release. The *ex-vivo* drug permeation study showed 1.85 folds increment in intestinal permeability as compared to IBH tablets. The *in-vivo* anti-anginal efficacy studies were performed using vasopressin-induced angina model in Wistar rats. Developed formulation was found to have a therapeutic effect for three days.

1. Introduction

Coronary heart diseases (CHD) are a matter of concern for the globe due to rising mortality and morbidity cases. The deaths and disabilities due to CHD are increasing continuously in developing countries; however, declining in developed countries [1]. According to the World Health Organization (WHO), South Asia region has one of the highest CHD mortality rates in the world [2,3]. Stable angina is one of the outcomes of CHD that causes uneasiness/pain in the chest. It arises when cardiac muscles do not get enough blood supply; one or more blood arteries gets narrowed or blocked. Angina causes pain and discomfort in the neck, jaw, shoulder, back or arm.

Ivabradine Hydrochloride (IBH) is a recently approved medicine for stable angina and chronic heart failure management-lowering the heart rate. It works by inhibiting “funny channels” present in SA-node. In 2005, IBH tablets were approved by the European Medicines Agency; US FDA in 2015. The marketed dosage form (tablet) was found to have the following technical setbacks: oral bioavailability (35%–40%), half-life (2 h), and First pass metabolism (> 50%) by enzyme CYP3A4. As far as safety is concerned, the clinical trials of the approved product have shown the following side effects: bradycardia, hypertension, atrial fibrillation, temporary vision disturbance (flashes of light), dizziness, weakness or fatigue. In order to solve the aforementioned unmet needs, we have come up with a new strategy *i.e.* Ivabradine Hydrochloride loaded polymeric nanoparticles (IBH-PNPs). Polymeric nanoparticles could be an alternative to reduce the drawbacks associated with IBH

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