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Verapamil hydrochloride loaded solid lipid nanoparticles: Preparation, optimization, characterisation, and assessment of cardioprotective effect in experimental model of myocardial infarcted rats

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ABSTRACT

Verapamil, a calcium channel blocker has poor bioavailability (20–30%) owing to extensive hepatic first-pass metabolism. Hence, the major objective of this research was to improve the oral bioavailability of Verapamil by Solid Lipid Nanoparticles (V-SLNs) using high shear homogenization and ultrasonication technology. A 3^2 factorial design was employed to statistically optimize the formulation to get minimum particle size with maximum entrapment efficiency. The average particle size was 218 nm and the entrapment efficiency was 80.32%. The V-SLN formulation exhibited biphasic behavior with a rapid release at first, then a steady release (75–80%) up to 24 h following the Korsmeyer Peppas release model. In the Isoproterenol induced myocardial necrosis model, oral administration of V-SLNs positively modulated almost all the studied hemodynamic parameters such as left ventricular end-diastolic pressure, cardiac injury markers, and tissue architecture. The cardioprotective effect was also confirmed with histopathological studies. When compared with free drugs, in-vivo pharmacokinetic studies demonstrated a rise in $t_{1/2}$, $AUC_{0-\infty}$, and Cmax, indicating that bioavailability has improved. These encouraging results demonstrate the promising potential of developed V-SLNs for oral delivery and thereby improve the therapeutic outcome.

1. Introduction

Verapamil is a well-known drug classified as an L-type calcium channel blocker that exhibits antiarrhythmic, antianginal, and antihypertensive effects [1,2]. By inhibiting calcium influx, vascular smooth muscles do not contract, resulting in reduced blood vessel resistance and lower blood pressure throughout the peripheral circulation. Reducing vascular resistance decreases the force against which the heart must push, lowering the amount of energy being expended by the heart and reducing oxygen requirements [3]. Verapamil is BCS Class I drug with good absorption (≤ 90%) from the gastrointestinal membrane after oral administration, still it faces the problem of only 20–35% systemic bioavailability. The low and variable bioavailability is reported to be due to extensive first-pass metabolism

Abbreviations: EE, Entrapment Efficiency; FTIR, Fourier-transform infrared spectroscopy; DSC, Differential Scanning Calorimetry; PS, Particle size; PDI, Polydispersity Index; SLN, Solid lipid nanoparticles; SEM, Scanning Electron Microscopy; V-SLNs, Verapamil hydrochloride loaded Solid lipid nanoparticles; ISO, Isoproterenol; SAP, Systolic arterial blood pressure; DAP, Diastolic arterial blood pressure; MAP, Mean arterial blood pressure; LVEDP, Left ventricular end-diastolic pressure; CK-MB, Creatine Kinase in muscle and brain; LDH, Lactate Dehydrogenase.

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