ABSTRACT

Osteoporosis is the most common type of bone disease, characterized by low bone mass density, micro-architectural deterioration of bone and a consequent increase in fracture risk. Risedronate sodium and Atorvastatin calcium were selected as drug candidates for the treatment of osteoporosis. Atorvastatin calcium is a specific inhibitor of the HMG-CoA reductase enzyme, inhibiting osteoclast growth and encouraging osteoblast activity through increased BMP-2 protein production. Risedronate sodium works by inhibiting bone resorption, thereby helping to maintain bone density and reduce the risk of fractures. Atorvastatin calcium and risedronate sodium have several limitations, including gastrointestinal disturbances and low oral bioavailability due to first-pass metabolism, low aqueous solubility (in the case of atorvastatin calcium), and unabsorbable complex formation of the drug with divalent atoms (in the case of risedronate sodium). These limitations were overcome by formulating glycerosomes and polyelectrolyte complex nanoparticles that were incorporated in transdermal patches for bioavailability enhancement via the transdermal route.

The **aim of present work** was to formulate, optimise, and evaluate anti-osteoporotic drugs loaded nanocarriers for the treatment of osteoporosis by enhancing permeability and bioavailability through the transdermal route. The **present work hypothesized** that the transdermal patches containing drug-loaded nanocarriers (glycerosomes and polyelectrolyte nanoparticles) for the treatment of osteoporosis will enhance the permeability of the drug through the skin membrane and deliver it to the bloodstream, which in turn will enhance the bioavailability of Risedronate sodium and Atorvastatin calcium.

The drug loaded glycerosomes were prepared by the lipidic thin film hydration method and optimized by a definitive screening design. Whereas PECN were prepared by the ionic gelation method and optimized by Box-Behnken design. The optimized glycerosomes/PECN were evaluated for physicochemical characteristics such as vesicle/particle size, polydispersity index, zeta potential, % entrapment efficiency, % drug loading capacity, transmission electron microscopy, differential scanning calorimetry, FTIR, X-ray diffraction, in vitro drug release study, ex vivo skin permeation study, in vitro cell line study, and stability study. The optimized glycerosomes/PECN showed desired physicochemical properties, better skin permeability of the drug, sustained drug release, better cell viability, and longer stability.

The optimized atorvastatin calcium/risedronate sodium loaded glycerosomes/PECN were incorporated into the transdermal patch by solvent evaporation method. The optimized

transdermal patches were evaluated for physicochemical characteristics, ex vivo skin permeation study, skin uptake study by fluorescence microscopy, skin integrity study by FTIR, histopathology study, and stability study. The glycerosomes/PECN incorporated transdermal patch showed better permeability of the drug through the skin, longer stability, and no change in skin integration. The developed transdermal patches showed no skin damage after application.

The developed atorvastatin calcium/risedronate sodium loaded glycerosomes/PECN incorporated transdermal patches were subjected to pharmacokinetic study. The results of the pharmacokinetic study showed that the developed formulations enhanced bioavailability as compared to marketed formulations. In pharmacodynamic study, osteoporosis was induced in female rats by bilateral ovariectomy surgery after 90 days. The osteoporosis-induced rats were treated with developed formulations as well as marketed formulations for 30 days. The results showed that the developed formulation had more anti-osteoporotic activity as compared to the marketed formulation.

The overall results of the presented work concluded that the prepared atorvastatin and risedronate sodium-loaded glycerosomes and polyelectrolyte complex nanoparticles incorporated into the transdermal patch are promising drug delivery systems for the selected poorly bioavailable drugs and demonstrated enhanced anti-osteoporotic activity.