Nanocrystal Formulation of Lercanidipine by Simple Evaporative Antisolvent Technique

N. Udupa¹, Ankita Chonkar¹, J Venkata Rao²

Department of Pharmaceutics¹, Department of Pharmaceutical Biotechnology²; Manipal College of Pharmaceutical Sciences, Manipal University, Manipal, India

ABSTRACT SUMMARY

Lercanidipine HCl nanocrystals were formulated by evaporative antisolvent method. Methanol was used as solvent as it showed highest solubility of lercanidipine. The polymers/surfactants were dissolved in water separately and the resulting mixture was stirred at 10,000 rpm using a high speed homogenizer at the temperature of 10ºC. After formation of a homogenous aqueous solution, the drug solution was added with continuous stirring, followed by bath sonication. The smallest particle size was found to be 35 nm

INTRODUCTION

Nanocrystals have greater surface/volume ratio which results in improvements in dissolution and enhanced permeability. They also may provide means of bypassing the liver, thereby preventing the first pass metabolism. Ultimately nanocrystallization may enhance the bioavailability of lercanidipine. Lercanidipine HCl, a novel dihydropyridine calcium-channel blocker, is used alone or with an angiotensin-converting enzyme inhibitor, to treat hypertension, chronic stable angina pectoris, and Prinzmetal's variant angina. According to clinical and preclinical findings, though lercanidipine possess favorable efficacy and tolerability profile with protective effects on the kidneys and cardiovascular system, when orally administered it exhibits non-linear pharmacokinetics. Due to lower aqueous solubility (<5µg/mL), extensive first pass metabolism, low permeability and food dependent absorption in GI tract absolute bioavailability of Lercanidipine HCl is only 10%. Also it has slow onset of action. Here attempt has been made to develop nanocrystalline lercanidipine by simple evaporative antisolvent technique. Nanocrystalline particles are a suitable delivery system for all commonly used routes of administration i.e. oral, transmucosal and topical applications. In addition, aqueous dispersions of nanocrystals can be post-processed into tablets, capsules and fast-melts for various applications.

EXPERIMENTAL METHODS

Lercanidipine nanoparticles were prepared by evaporative antisolvent precipitation technique. Preliminary studies were carried out to investigate the solubility of Lercanidipine in various solvents. Methanol showed highest solubility of lercanidipine. 50 mg of lercanidipine was dissolved in sufficient volume (500 µl) of methanol. The polymers/surfactants were dissolved in water (10 ml) separately and the resulting mixture was stirred at 10,000 rpm using a high speed homogenizer at the temperature of 10ºC (Polytron Kinematica). Polyethelene glycol (PEG), hydroxy propyl
methyl cellulose (HPMC E5), hydroxy propyl cellulose (HPC), poly vinyl alcohol (PVA), methyl cellulose (MC), sodium alginate, pluronic F127 (PlurF127), sodium lauryl sulphate (SLS), tocopherol polyethylene glycol succinate (TPGS) were selected as stabilizers.

After formation of a homogenous solution, the drug solution was added all at once with continuous stirring for 15 minutes at 10,000 rpm. The suspension was kept to allow the foam to dissipate and then bath sonicated at frequency 53 Khz, 90% power for 10 min.

RESULTS AND DISCUSSION

Lercanidipine formulated into nanocrystals was found in the particle range 200-500 nm with majority of stabilizers. The PDI was approximately 0.2-0.3. The stabilizer’s characteristics play an important role in creating a stable formulation. It must be capable of wetting the surface of the drug crystals and providing a steric or ionic barrier. PEG is a nonionic, low molecular weight stabilizer which showed increase in the particle size against blank (nansuspension without stabilizer) due to adsorption of the stabilizer on drug surface. Increase in the amount of stabilizer led to increase in the particle size due to formation of thicker adsorption layer. Same phenomenon was observed in case of HPMC, MC, HPC, Sodium alginate. Higher the viscosity of the stabilizer more is the thickness of adsorption layer on the drug particle resulting in higher particle size. These nanosuspensions with PEG, HPMC exhibited good short term stability but nanosuspensions with sodium alginate, HPC, MC exhibited sedimentation due to larger particle size.

Poloxamer-407 proved to be effective stabilizer in reducing particle size of the drug and particle size reduced with the increase in the concentration of Poloxamer-407. It is reported that Poloxamer-407 can form a substantial mechanical and thermodynamic barrier at the interface that retards the approach and coalescence of individual molecules.

In case of PVA, decrease in the particle size was observed with increasing concentration of PVA. It might be due its flexible adsorption film forming nature on drug particles. But comparatively larger particle size was obtained by PVA. This might be because the turbulence created by high speed homogenization is not sufficient in case of PVA which causes rapid nucleation and breakdown of the crystals which prevents nanocrystals from growing to a larger size.

SLS and TPGS are anionic and nonionic stabilizers which offer ionic and steric stabilization to prevent coalescence of individual molecules.

![Particle Size Distribution](image-url)
Conclusion

Lercanidipine nanosuspensions were prepared by simple evaporative antisolvent technique with drug loading of about 5mg/mL. The drug loading was 1000 times more than its solubility in water. These nanocrystals can be easily scaled up into solid oral dosage forms to decipher the problems associated with the oral administration of lercanidipine and ultimately to enhance the bioavailability.

References


Acknowledgement

We thank the authorities of Manipal University for providing TMA Pai research grant and Manipal College of Pharmaceutical Sciences for providing necessary facilities to carry out the work.